IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Review Article**
October 2023 Vol.:28, Issue:3


# Immuno-Oncology: Unleashing the Power of the Immune System against Cancer

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

**Sohom Manna, Priyanka Ray*, Prapti Chakraborty**

*Gurunanak Institute of Pharmaceutical science & technology*
*157/f Nilgunj Road,Sodepur ,Panihati,Kolkata -114, West Bengal, India*

**Submitted:** 21 September 2023
**Accepted:** 28 September 2023
**Published:** 30 October 2023



**Keywords:** Immuno-therapy, NK-cells, T-cell receptors, Immune checkpoints, Cancer-specific antigens, Antigen-presenting cells (APCs), Immuno-Editing, Cytokines, CAR-T cells, CTLA-4.

## ABSTRACT

The need for new therapeutic approaches is growing as cancer continues to be a major worldwide health burden. Immuno-oncology represents a revolutionary approach to cancer treatment by utilising the complex interaction between the immune system and tumour cells. In recent years, this rapidly evolving field has witnessed remarkable advancements with immunotherapeutic approaches showing unparalleled efficacy in treating a range of cancers. However, cancer cells can avoid immune identification and suppress immunological reactions, which promotes the growth and development of tumors. The goal of immuno-oncology is to overcome these difficulties by improving the immune system's capacity to identify and effectively eliminate cancer cells. This review focuses on the many immune system elements, including innate immune cells like macrophages and natural killer cells as well as adaptive immune cells like T cells and B cells, that are involved in the detection and eradication of cancer. The intricate relationships involving immune checkpoint pathways, tumor microenvironment interactions, and cancer cells and the immune system are also discussed. The advancements in immuno-oncology, including immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell treatment, and cancer vaccines, will also be covered in this article. The paradigms of cancer treatment have been completely altered by these advanced therapeutic techniques, which have shown extraordinary efficacy in treating a range of malignancies. Additionally, the difficulties with immuno-oncology have also been addressed here, including immune-related side events and resistance mechanisms. For the advancement of cancer immunotherapies that are both safer and more effective, it is essential to comprehend these difficulties. Lastly, this review will emphasize current research initiatives and immuno-oncology's future directions. The area is still developing quickly and is now offering patients with cancer new hope with personalized immunotherapy and combination medicines. In conclusion, this in-depth review paper highlights the crucial role of immunology in the treatment of cancer, with an emphasis on immuno-oncology. Immuno-oncology has become a potential strategy for increasing the immune system's capacity to identify and destroy cancer cells. Future developments in cancer treatment and the field of immuno-oncology will surely benefit from a fuller comprehension of the intricate relationship between cancer and immunity.

## INTRODUCTION:

The immune system's main function is to identify and eliminate cells that are genetically unstable and have a tendency to turn into cancer cells if ignored. [1]

The immune system can specifically destroy tumor cells without harming other healthy cells and has long-term memory that can stop cancer from coming back. [2]

Over the past decade, it has been shown that boosting immune responses can be a good approach in the treatment of cancer. The main goal of Immuno-oncology is to develop and administer treatments that enhance the natural capacity of the human body to develop efficient immune system response over cancer cells. [3]

Immune-oncology works by utilizing the human's innate immune function for identifying and eliminating cancer cells. This method is known to be a minimally toxic method compared to other conventional methods. When this approach is combined with traditional therapies, it shows encouraging improvements in patients. [4]

### An overview of Immuno-oncology's history and background:

### Statistics about cancer:

One of the main causes of death in the globe is cancer. Around 14 million new cases and 8.2 million deaths due to cancer occurred globally in 2012. Within the next twenty years, there will be about 22 million additional cases of cancer. [7,8]

Africa, Asia, and South and Central America account for more than 60% of all new cases of cancer and 70% of all cancer-related deaths worldwide.

In the US, about 1.6 million new instances of cancer were reported in the year 2015, while the number of deaths was 589,430. Globally, there will be roughly 10 million fatalities in 2020. [9,10,11,12]

### Immuno-oncology's historical development:

Immuno-oncology has been a concept since 1893. In that year, American surgeon and cancer researcher William Coley noticed cancer recovery among patients having postoperative bacterial infections and hypothesized that immune system activation may be a factor in the fight against cancer. Paul Ehrlich subsequently proposed in 1909 that the body's immune

system must be crucial in blocking the development of cancer. In the middle of the 20th century, Lewis Thomas along with Frank MacFarlane Burnet proposed the theory that immune surveillance - a method by which the immune system can destroy cancerous cells; is dependent on the immune system's ability to recognize tumor-associated antigens. [22,23,24,25,26]

The idea of immune monitoring later developed into "immunoediting," reflecting the capacity of tumor cells to elude the immune system, according to the laboratory work done by Lloyd Old along with Robert Schreiber. Numerous new therapeutic targets have been found as the knowledge of the fundamental processes of immunoediting advances. Immune checkpoint inhibition, which James Allison initially demonstrated in the 1990s, is one such target that is currently showing promise in clinical settings. The journal Science named cancer immunotherapy as the "breakthrough of the year" in 2013. [27,28,29,30]

### ❖ What is cancer?

Cancer is defined as the abnormal and uncontrolled proliferation of a group of cells. These cells are known as cancer cells and the abnormal growth of tissue is also called as neoplasm. The cancer cells can spread throughout the whole body through the blood or lymph system by the metastasis process. Carcinogens are substances or agents that can cause uncontrolled multiplication inside our body, such as alcohol, tobacco, radiation, cadmium, vinyl chloride etc. The main characteristics of cancer cells are uncontrolled proliferation, differentiation and loss of function, invasiveness and metastasis. Cancer arises due to several changes; such as, the inactivation of tumor-suppressor gene and the activation of oncogenes. [13,14]

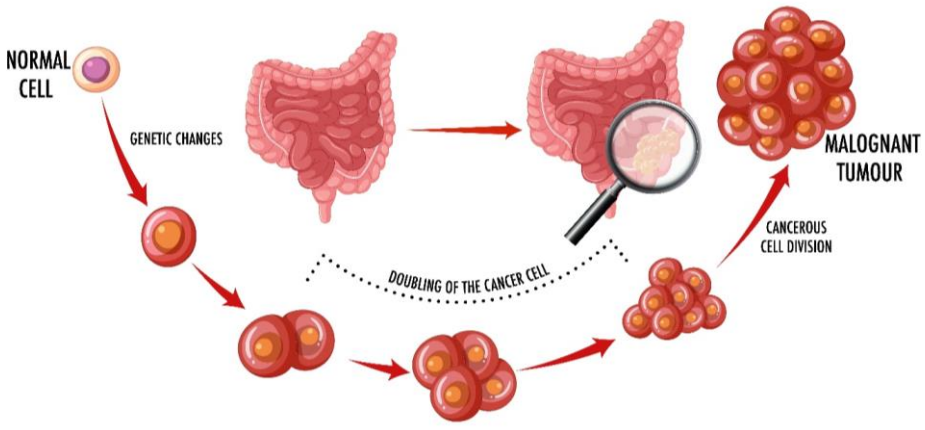


**FIG 1: Cancer Development Process** [43]

- **Tumor cells:**

Tumor cells are different from the body's normal healthy cells. When mutations cause normal cells to continue to grow and proliferate uncontrollably, the cells turn neoplastic. These cells can invade into neighboring tissues and move to other parts of the body. There are mainly two types of tumor such as, benign tumors, in which the tumor cells cannot spread by metastasis, they grow locally and, malignant tumor, in which tumor cells spread throughout the body by invasion or metastasis. [13,14]

**Immune cells:**

There are several inflammatory immune cells present in our body. These cytotoxic innate and adaptive immune cells can regulate the formation of tumors [6]. Different receptors and ligands are located on the interfaces of immune cells and tumor cells. These ball and cup structured receptors and ligands act as targeting sites in immune-oncology treatments. Immune cells and tumor cells both have receptors and ligands such as immune checkpoint receptors, which are present on the T-cells' surface. Immunologic receptors bind to the ligand and show an immune response in the body. As an example – the PD-1 receptor interacts with PD-L1 ligand. [5]

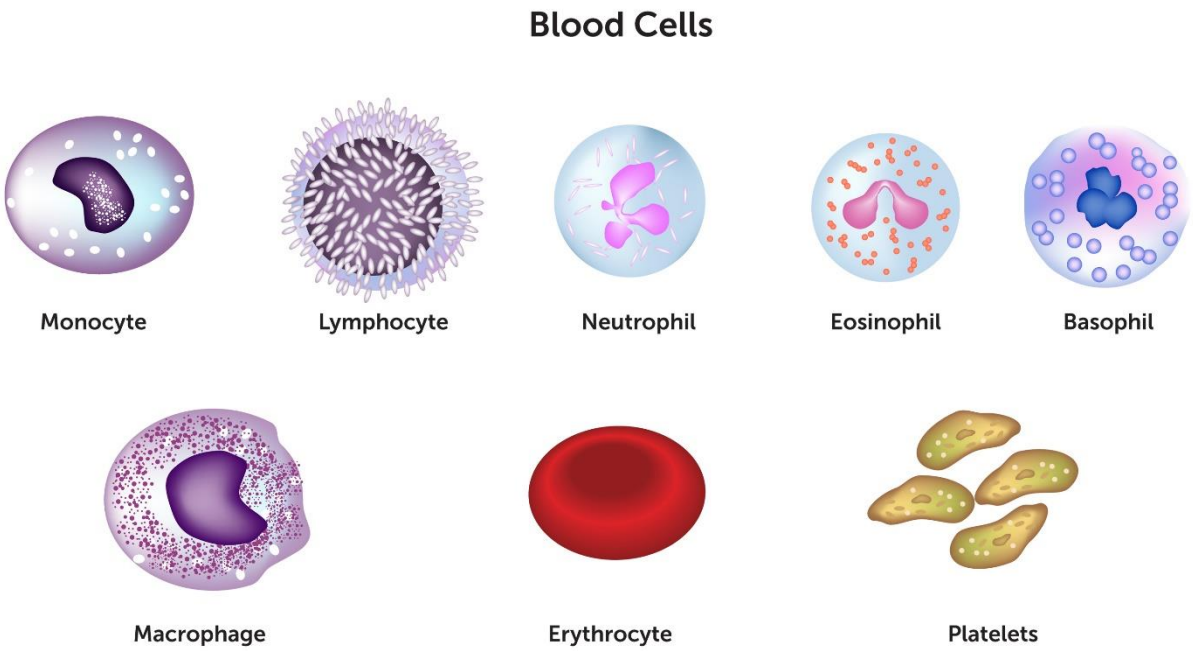


**Fig 2: Immune cells** [45]

**Immune system:**

The body's defense against attacks from foreign pathogens is provided by the immune system, which is a network of cells, tissues, and organs. Our immune system's main function is to protect the body from disease-causing harmful microorganisms; which include bacteria, viruses, fungi etc. Innate immunity and adaptive immunity are the two defence mechanisms that make up the immune system. [17,51]

**Innate Immunity:**

The initial line of defense against an invading infection is innate immunity. The host employs this defense mechanism as soon as possible after coming into contact with an antigen, usually within hours. The following cells play a role in the innate immune response: The NK (Natural Killer) Cells, the dendritic cells, basophils and mast cells, the phagocytes, etc. The first line of defenses are the skin, mucous membranes of the throat, gut, etc. [51]

**Adaptive Immunity:**

When innate immunity fails to completely eradicate pathogenic microbes, adaptive immunity emerges. The term "acquired immunity" also applies to adaptive immunity. This defense mechanism is dependent on the antigen; that means as soon as the cell gets exposed to the antigen, no reaction happens right away. The body produces a variety of antibodies to diverse infections as a result of vaccines and responses to different diseases. [51]

**Different types of Immune Cells:** [17,51]

There are many different parts that make up the immune system, including White blood cells, the bone marrow, the lymphatic system; the thymus, the tonsils, adenoids etc. Both the innate and adaptive immune systems comprise a large number of interconnected cells, these are called Immune cells. The lymphocytes (T cells, B cells, and NK cells), neutrophils, and monocytes/macrophages are the main type of cells in the immune system. Each of them is a subtype of white blood cell.

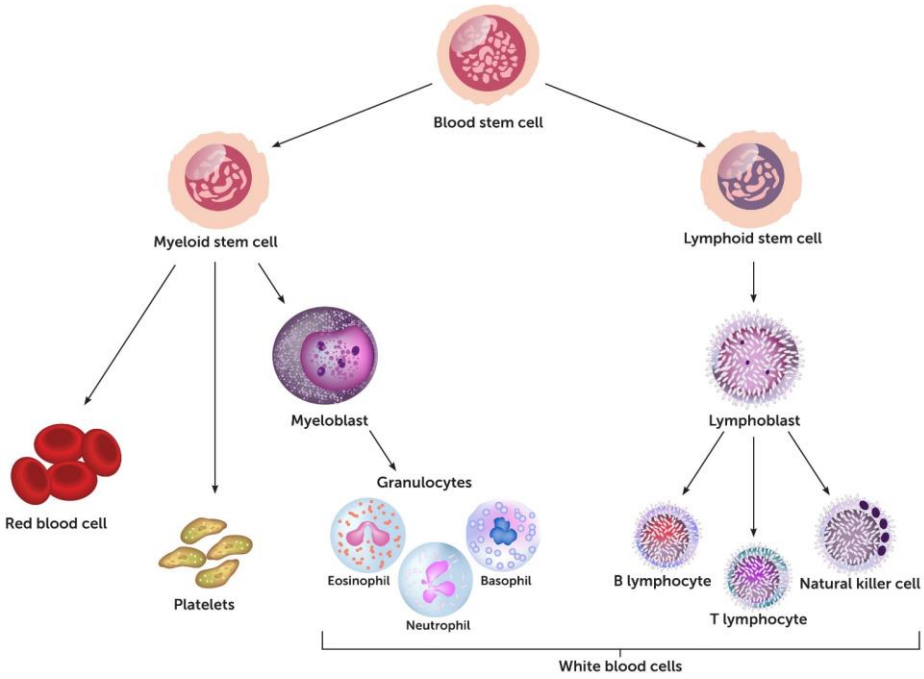


**FIG 3: Different types of immune cells** [45]

**1) White blood cells:**

White blood cells, also known as leukocytes, are a diverse group of immune cells that are in charge of locating and removing of pathogens. White blood cells often fall into a few categories:

**A) The lymphocytes:**

**i) B cells:**

B cells, also known as B lymphocytes, are specialized immune system cells whose primary objective is to create antibodies (immunoglobulins). In the bone marrow, stem cells give rise to B cells. B cells are programmed as part of their regular development in the bone marrow to not make antibodies against healthy tissues. B cells are located in the bloodstream, lymph nodes, spleen, bone marrow etc after full development.

B cells are responsible for producing antibodies, proteins that bind to specific antigens and neutralize or mark them for destruction. This process is known as humoral immunity. Contrary to T cells, B cells have specific antibodies produced on their cell surfaces that enable them to recognize antigens without the help of APCs.

**ii) T Cells:**

T cells are unaware of free-floating antigens, in contrast to B cells. Instead, they have specialized receptors that resemble antibodies and can detect antigen fragments on the outermost layers of infected or malignant cells.

T cells support immune defenses in two main ways: some of them direct and control immunological responses, while others go straight for diseased or malignant cells.

Hematopoietic stem cells in the bone marrow are the source of T cells, which migrate and mature in the thymus afterward. There are several different subtypes of T cells, including regulatory, cytotoxic, and helper T cells. Helper T cells encourage the productive performance of other immune cells, including B cells and cytotoxic T cells. Whereas regulatory T cells work to keep the immune system in balance and limit overreactions, cytotoxic T cells attack and eliminate infected or abnormal cells directly.

**B) Phagocytes:**

The phagocytes are a type of big white blood cells with the ability to engulf and digest microorganisms.

Through a process known as phagocytosis, phagocytes such as macrophages, and dendritic cells absorb and kill invading microbes. By exposing the immune system to antigens, which are substances generated from infections, they also help to activate additional immune cells.

• Monocytes are phagocytic cells that move throughout the bloodstream and when they travel to tissues, they can transform into macrophages and dendritic cells.

• Macrophage is crucial to the functioning of the human immune system. They perform several tasks, such as engulfing and digesting pathogens, removing waste products and dead cells, and activating other immune-system cells.

• Antigens are captured by dendritic cells, which then go to lymph nodes and transmit the antigens to other immune cells, triggering immunological responses.

**C) Granulocytes:**

Granulocytes are one type of White blood cells, that have tiny granules which produce enzymes when the body's immune system is attacked. In bone marrow, granulocytes are produced from stem cells.

Granulocytes come in three different subtypes. These include basophils, neutrophils, and eosinophils.

**a) Basophils**: Basophils play a role in inflammatory reactions. The main role of these granulocytes is to prevent allergic responses. They release heparin, which is a blood thinner; It prevents clotting, as well as histamine, which transports allergens to leave the body.

**b) Neutrophils**: Neutrophils are a special kind of granulocyte, or white blood cell, that are essential for the body's innate immunological response. Because neutrophils are powerful phagocytes, they can ingest or engulf and eliminate foreign substances including bacteria, fungus, and cell debris.

**c) Eosinophils:** Eosinophils are predominantly parasite-focused and play a crucial role in allergic responses and asthma. To eliminate parasites and alter immune responses, they emit poisonous proteins and other chemicals.

**2) Natural Killer (NK) Cells: [20]**

Another deadly white blood cell is the natural killer (NK) cell. NK cells are loaded with granules containing powerful chemicals, similar to killer T cells.

NK cells are essential to the innate immune response. They are in charge of detecting and removing malignant and contaminated cells without prior sensitization.

Main functions of NK cells are to find and remove aberrant cells (cancerous cells or virally contaminated cells); Cytotoxic action caused by the discharge of cytotoxic agents; Cytokine production to control the immune response and improve immune cell activity.

**3) Mast Cells:** The Mast cells are one type of tissue-resident immune cells that are present throughout the body, especially in tissues like the skin and mucous membranes that come into touch with the outside world. They are essential in the development of allergic reactions and immunological responses to parasites. When mast cells are activated, chemical mediators like

histamine are released, which causes inflammation and draws in additional immune cells. [19]

**Different types of Tumor Cells:**

Neoplastic cells, commonly referred to as tumor cells, are aberrant cells that develop into a growth or tumor in the body. The growth rate, structure, and function of these cells are all different from those of normal cells.

Normal cells give rise to tumor cells after undergoing genetic mutations or DNA alterations. The usual controls that regulate cell division, growth, and death are interfered with by these mutations. As a result, unchecked division and proliferation of tumor cells cause a tumor to develop.

There are two basic categories of tumor cells: benign and malignant. Non-cancerous benign tumour cells often stay localized and do not spread to other body organs. They typically develop gradually and do not invade nearby tissues. In contrast, carcinogenic malignant tumour cells can infect neighbouring tissues and migrate to distant locations through a process known as metastasis.

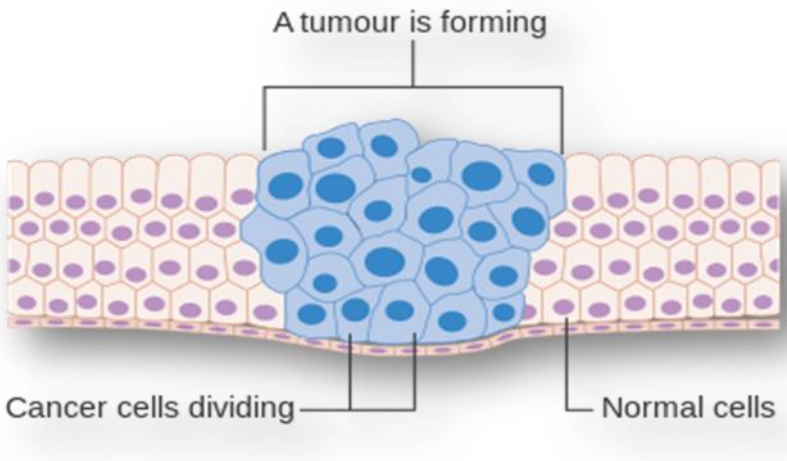


**FIG 4: Formation of tumour cells** [44]

**Immunity in Cancer: Immuno-oncology [21]**

Some specific antigens, on the outermost layer of normal cells that develop into cancerous cells, may change. The body's defense mechanisms, including as killer T cells, NK cells, and macrophages, become active if the immune system detects foreign invaders. However, the

immune system is limited in its ability to provide body-wide monitoring while removing any malignant cells. When the system malfunctions or is overburdened, tumors form.

Ingenious new anticancer weapons are being created by scientists by modifying immune cells and other chemicals. They are enhancing the patient's immune responses by employing compounds referred to as biological response modifiers, such as lymphocytes and lymphokines. Biological response modifiers may occasionally be injected right into the patient. Additionally, part of the patient's lymphocytes can be modified in the lab to become tumor-hungry cells, that are subsequently injected into the body of the patient to fight the disease.

Nowadays, It is possible to combine cancer-specific antibodies with medications, toxins, or radioactive substances, then transport them toward the intended cancerous cells. As another option, toxins can be coupled with a lymphokine and transported to cells that have lymphokine receptors. Antibodies that have been radioactively identified can also be used to find metastatic cancerous cells that have spread undetected.

Researchers are currently conducting trials on therapeutic cancer vaccines, which distinguish themselves from conventional vaccines. Unlike traditional vaccines administered as a preventive measure before disease occurrence, cancer vaccines are utilized after the emergence of cancer with the objective of aiding the immune system in combating the illness. Typically, the immune system exhibits a weak or non-existent response to cancer cells. Cancer vaccines aim to enhance the innate anticancer reaction by provoking robust killer T-cell responses against tumors. While these vaccines alone are generally incapable of eradicating a tumor, studies indicate their potential effectiveness when used in conjunction with other treatment modalities.

**The Tumour Microenvironment's Immunological Landscape:** [38]

Immuno-oncology relies heavily on an understanding of the intricate interactions among the body's immune system and the tumor microenvironment. The extracellular matrix, stromal cells, immune cells, and cancer cells make up the dynamic ecology known as the tumor microenvironment. This complex environment affects the development, progression, and therapeutic response of the tumour.

**1) Immune Cell Infiltration:** The presence and composition of immune cells in the tumour microenvironment are crucial to the growth of tumors and their response to therapy. T cells,

B cells, natural killer cells, or NK cells macrophages, and dendritic cells are examples of immune cells that can either stimulate or inhibit anti-tumor immune responses. The significance of an active immune reaction is demonstrated by the association of high tumor-infiltrating lymphocyte (TIL) counts with improved prognosis in a variety of malignancies.

**2) Immunological Suppression and Immune Checkpoints:** Tumours have evolved complex defense mechanisms to avoid immunological monitoring and inhibit anti-tumor immune reactions. Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) are examples of immunological checkpoints that function as brakes on the immune system to avoid over-activation and immune-mediated tissue damage. Tumors, however, use these checkpoints to avoid immune eradication. Checkpoint inhibitors have demonstrated significant success in reactivating anti-tumor immunological responses and enhancing patient outcomes by specifically targeting immunological checkpoints. [47]

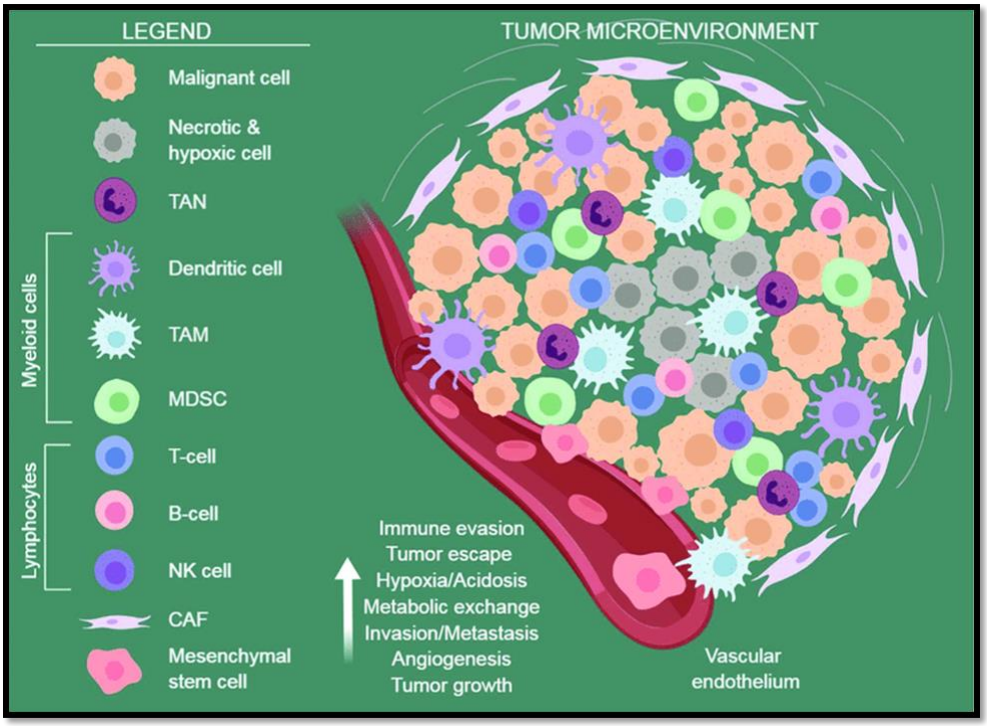


**FIG 5: Tumor Microenvironmen**

**3) Tumor-Associated Macrophages (TAMs):** Macrophages play a significant role in the immune cell infiltration of the tumor microenvironment. Macrophages can have either anti-tumor (M1) or pro-tumor (M2) characteristics depending on how they are polarised. While M1-like TAMs have anti-tumor activity, M2-like TAMs frequently promote tumour development, angiogenesis, and suppression of the immune system. A potential method for

restructuring the immune system and improve anti-tumor immune responses is to alter the polarisation of TAMs.

**4) Cytokines that modulate immune responses in the tumour microenvironment:** Cytokines are mobile signaling molecules that control immune responses. Different cytokines, including interferons, interleukins, and the tumour necrosis factor (TNF), which may exhibit both pro-inflammatory as well as immunosuppressive effects, are secreted by immune and tumour cells. It is crucial to understand the cytokine milieu inside the tumour microenvironment in order to customize immunotherapeutic approaches and effectively modulate immune responses.

**5) Immunometabolism:** Immune cells' metabolic status within the tumor microenvironment has a significant impact on how they function and their anti-tumor efficacy. Immune cell activity is hampered by the metabolic changes that tumour cells frequently adopt, which produce an immunosuppressive environment. Reprogramming the immunometabolic environment and boosting anti-tumor immune responses may be accomplished via approaches which target pathways of metabolism within both immune and tumor cells.

In conclusion, tumor growth, progression, and therapeutic response are significantly influenced by the immunological milieu of the tumour microenvironment. For the creation of new immunotherapeutic strategies, understanding the complex interactions among immune cells, tumor cells, and stromal components is essential. It is possible to increase the effectiveness of treatment and advance precision medicine in oncology by manipulating the immunological landscape by attacking immune checkpoints, controlling immune cell infiltration, and changing the cytokine milieu.

**Cancer-Immunity Cycle:** [15]

The Cancer-Immunity Cycle encompasses a sequential progression of events that are essential for a successful immune response against cancer cells. It involves the initiation and iterative expansion of a series of steps, ensuring the effective elimination of cancerous cells.

The way the immune system responds to cancerous cells is a cyclical process that, in theory, may be self-replicating, resulting in an intensified immune response. Natural killer (NK) cells first identify cancer cells, and when they come into contact with certain ligands on the surface of the cancer cells, the cancer cells are destroyed. As a result, antigen-presenting cells (APCs)

such as dendritic cells and other APCs secrete cytokines, which in turn prime T cells in lymphoid tissue to become activated.

When these cytotoxic T cells reach the tumor, they attach to the Class I MHC proteins on the surface of cancer cells and destroy the target cancer cells by binding to them. This then triggers the release of additional antigens, enhancing the immunological response.

Nevertheless, there are numerous regulators at each stage of the procedure, positive as well as negative. The adverse regulators have the ability to create feedback loops that weaken or stop the immune response. These pathways may not only help the tumor cell avoid immune response but may also hasten tumour development.

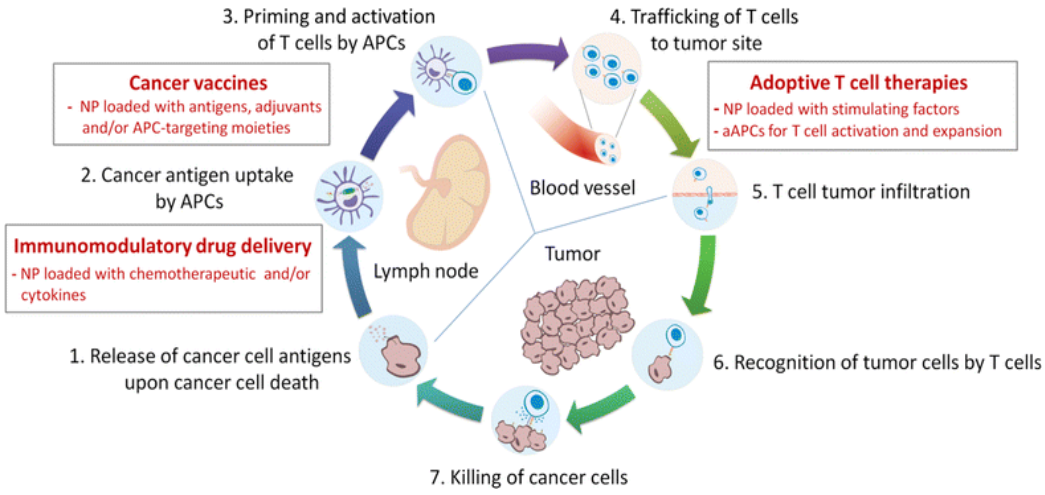


**FIG 6: Cancer-Immunity Cycle** [46]

The steps of the cancer-immunity cycle are:

**1) Release of Cancer Antigens:** Cancer-specific antigens, molecules found on the surface of cancerous cells, are released to start the process. These antigens act as markers that warn the immune system when malignant cells are detected.

**2) Antigen Presentation:** Cancer antigens that have been released are captured by antigen-presenting cells (APCs), such as dendritic cells. They prepare and deliver the antigens to T cells and other immune system effector cells. For the T cells to identify and launch an immune attack against cancer cells, this presentation is necessary.

**3) T Cell Priming and Activation:** When cancer antigens are presented, they specifically prime and activate particular T cells, especially CD8+ cytotoxic T cells. This priming

procedure improves the T lymphocytes' capacity to identify and attack cancer cells that express the same antigens.

**4) T-cell trafficking:** T-cell trafficking to the tumor is the migration of primed and activated T lymphocytes towards the direction of the tumor cite.

**5) Tumour Infiltration:** After T-cell trafficking, they infiltrate the micro-environment around the tumour. The direct interaction between T cells and cancerous cells is made possible by this invasion.

**6) Recognition and Binding:** T cell receptors (TCRs) interact with cancer antigens on major histocompatibility complexes (MHCs) at the surface of cancerous cells in order to recognize and bind to cancer cells in the tumour microenvironment.

**7) Cancer cell eradication by activation of T-cell killing:** When T cells connect to cancer cells, a series of immunological reactions are set off, activating the T cells' killing capabilities. Inducing apoptosis (cell death) in cancer cells entails the production of cytotoxic chemicals such as perforin and granzymes.

When T cells are successfully activated, they multiply, which increases the number of cancer-specific T cells in the body. To mount a powerful immune response and successfully target cancer cells, multiplication is essential. Immune cells, including freshly multiplied T cells, travel away from the tumor site to other parts of the body where cancerous cells may be found. This procedure aims to stop the spread of metastatic lesions and stop the spread of malignancy. The infiltrated T cells identify new tumors at various sites and start the cycle all over again, causing more cancer cells to be destroyed. This continuous and ongoing immune monitoring against cancer is facilitated by this iterative approach. [15]

**The 'three Es' of immunoediting cancer cells:** [16, 30, 31,48]

The dynamic process through which the immune system can both shape and be shaped by tumours over time is referred to as immuno-editing, sometimes known as cancer immuno-editing.

The concept of immuno-editing is based on the understanding that the immune system can recognize and eliminate cancer cells as foreign entities. Cancer cells can come up with a number of ways to evade the immunological response, allowing them to survive and proliferate.

There are three stages in the immuno-editing process: Tumour immunoediting's "three Es" are:

**1) Elimination:** During this stage, the immune system detects and gets rid of any new cancer cells that appear. By releasing cytotoxic chemicals or triggering cell death, immune cells like natural killer cells and cytotoxic T cells can recognize and eliminate tumor cells. This stage is the beginning of the immune system's defense against cancer.

**2) Equilibrium:** Some cancer cells may survive the elimination phase and enter a period of equilibrium with the immune system, but the immune response is strong enough to prevent proliferation. By focusing on and regulating cancer cells during this phase, the immune system controls tumour progression. Cancer cells can, however, develop new mutations or alterations that give them the ability to avoid immune monitoring.

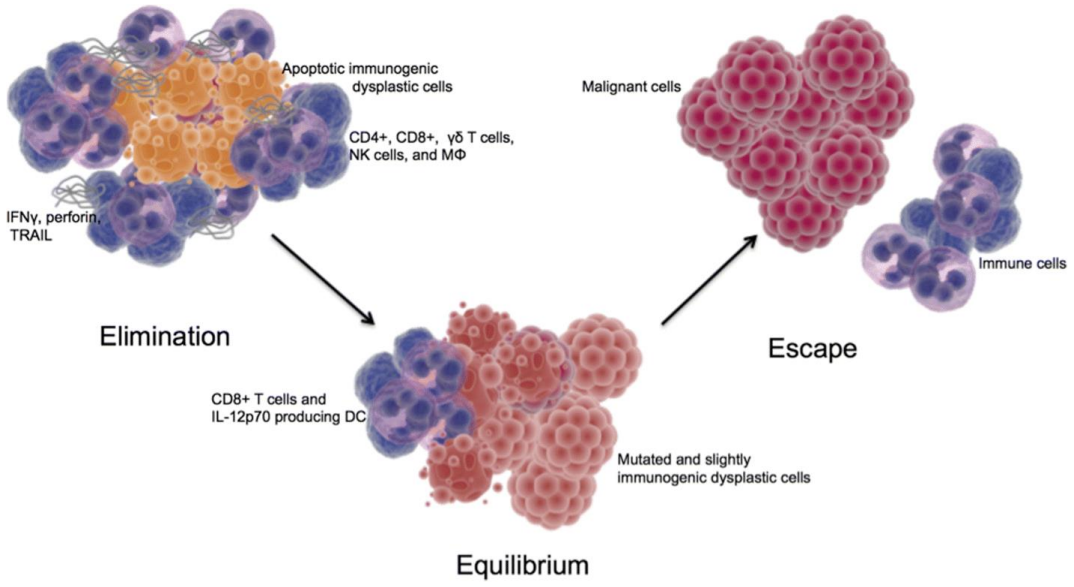


**FIG 7: Phases of Immuno-editing** [48]

**3) Evasion:** During the escape phase, cancer cells that are resistant to immune detection and destruction overgrow the immune system's ability to regulate them. These cells can create immune response-suppressing mechanisms, such as suppressing the expression of proteins involved in antigen presentation or triggering immunological checkpoint pathways, which can lead to clinically apparent disease.

**Tumors ability to avoid immunological attack:** [33,34]

There are several methods by which tumour cells can prevent immune responses.

• Dendritic cells or antigen-presenting cells might not be able to recognize cancer cell antigens.

• Cancer-specific effector responses may be replaced by regulatory T cell responses if cancer antigens are viewed as self-antigens rather than foreign substances.

• T lymphocytes might not be transported to the tumor or are stopped from interacting with it.

• Effector T cells may be suppressed by elements in the tumor microenvironment.

The immunological checkpoints for programmed cell death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are two of the main ways in which these effects are accomplished.

**A) PD-1 receptor Pathway:**

PD-1 receptors present on the outer surface of T cells. These receptors regulate the activation of T-cells. A number of cancer types, including melanoma and malignancies of the lung, kidney, head and neck, and colon, have been linked to an overexpression of this receptor's ligand, PD-L1. The immune response to cancer cells can be impacted in two different ways by the binding of this receptor to its ligand, PD-L1.

• In the lymph nodes, the increased expression of PD-L1 in immune cells that have infiltrated the tumour can stop new cytotoxic T cells from being primed and activated and, as a result, can stop these immune cells from being drawn to the tumor.

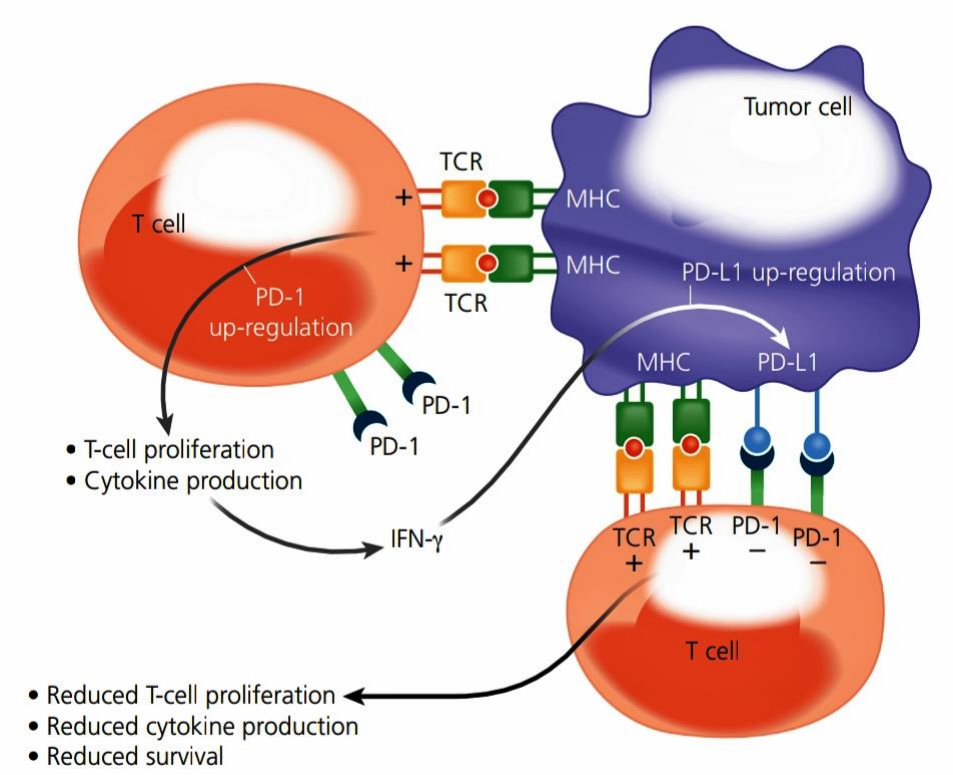


**FIG 8: PD-1 receptor's effects on functioning of T-cells** [16

• The increased expression of PD-L1 on cancer cells and immune cells like macrophages, dendritic cells, and T cells inside the tumor microenvironment results in the inactivation of cytotoxic T cells. In both situations, PD-L1 binding with PD-1 on the outer surface of T cells causes the establishment of T-cell tolerance, which is characterized by lowered cytokine production, decreased T-cell proliferation, and diminished antigen recognition. [33]

**B) The CTLA-4 pathway:**

CD80 (B7-1) and CD28-bound APCs and T cells provide positive co-regulatory (or co-stimulatory) signals that activate cytotoxic CD8+ T cells. Contrarily, when CD80 (B7-1) on the APC binds to CTLA-4 on the T cell, a negative signal is produced that reduces the generation of interleukin (IL)-2 by T cells and inhibits their ability to proliferate and survive. CTLA-4 is a crucial immune checkpoint and an ideal target for immunotherapy for cancer as a result. [34]

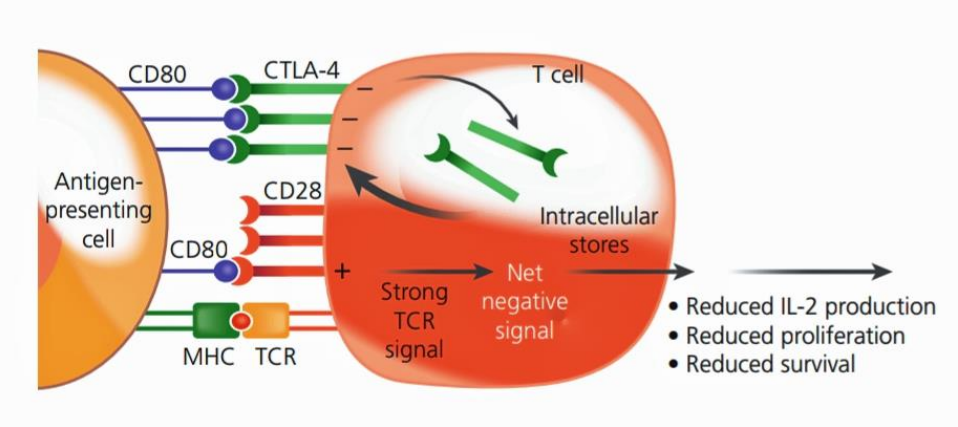


**FIG 9: Effects of CTLA-4 on the functioning of T-cell** [16]

**Immuno-oncology agents: [21]**

The main purpose of the immune system is to find and destroy aberrant cells, including cancerous cells. Cancer cells may find ways to avoid immune identification and decrease the immune response. Agents used in immuno-oncology interfere with these pathways and activate the body's immune response to identify and eliminate cancer cells. Drugs in the immuno-oncology class, also referred to as immunotherapies or immune checkpoint inhibitors or Immuno-oncology agents, are used to treat cancer by enhancing immune responses. Immuno-oncology drugs function by boosting the body's immune system to recognize and combat cancer cells, in contrast to conventional cancer treatments like chemotherapy, radiation therapy etc, that directly target cancer cells. Immune checkpoint blockage is one of the main tactics used by immuno-oncology drugs. Proteins on immune cells called immunological checkpoints control the immune response by limiting over-activation and preserving self-tolerance. Cancer cells, however, may alter these checkpoints to restrict the immune response. Immuno-oncology therapies disable these checkpoints so that the immune system can more effectively combat cancer cells.

**Different types of Immuno-Oncology Agents: [16,17,18]**

**1) Immune Checkpoint Inhibitors:** Immune checkpoint inhibitors have revolutionized cancer treatment. They function by preventing inhibitory substances that stop immune cells from attacking cancer cells, including programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Immune checkpoint inhibitors disable these molecules, allowing the immune system to function to its fullest capacity and effectively identify and eliminate cancer cells.

**2) CAR T-cell therapies:** In CAR T-cell therapy, the patient's own T-cells are modified to surface-express chimeric antigen receptors (CARs). These CARs are made to specifically target tumor antigens, enabling T lymphocytes to identify and destroy cancerous cells. Acute lymphoblastic leukaemia and diffuse large B-cell lymphoma are two hematologic cancers that have responded exceptionally well to CAR T-cell treatments.

**3) Vaccines for Cancer:** Cancer vaccines enable the immune system to identify and respond to cancer-specific antigens. Both preventive and therapeutic vaccinations fall under this category. Human papillomavirus (HPV) vaccinations are examples of preventive cancer vaccines that are designed to protect against specific forms of cancer. The immune system is stimulated against tumor antigens by therapeutic cancer vaccines, which are intended to treat cancer that has already spread.

**4) Cytokines:** Small proteins called cytokines control immune cell communication and functioning. Interleukin-2 (IL-2) and interferon-alpha (IFN-α) are two cytokines that have been utilized to boost the immune system in the treatment of cancer.

T-cell expansion and activation are encouraged by IL-2, but the immune response to cancer cells is strengthened by IFN-α.In some malignancies, like metastatic melanoma and renal cell carcinoma, these cytokines have proven effective.

**Combination therapies:** [16]

Combination drug therapy has become a potentially effective strategy in immuno-oncology therapies. The goal of immuno-oncology is to employ the immune system's ability to identify and destroy cancer cells. Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by preventing immune system-suppressing proteins, however, their efficacy in treating some tumours remains limited. By combining ICIs with other medications or treatment modalities, combination treatments aim to increase the effectiveness of ICIs and reduce resistance.

These are some examples of immuno-oncology combination drug therapies:

**1) Dual Immune Checkpoint Inhibitors:**

Combining two immune checkpoint inhibitors (ICIs) that target separate immune checkpoints, such as CTLA-4 and PD-1, has demonstrated enhanced response rates in several

malignancies. For the treatment of advanced melanoma, the combined administration of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) has been approved.

**2) Targeted therapies:**

ICIs may be used with targeted medicines that block particular signaling pathways implicated in the development and survival of cancer. For example, in patients with particular molecular abnormalities with non-small cell lung cancer (NSCLC), combining an EGFR inhibitor (e.g., gefitinib) or an ALK inhibitor (e.g., crizotinib) with an ICI (e.g., pembrolizumab) has demonstrated improved results.

**3) Chemotherapy:**

Conventional chemotherapy medications can alter the tumour microenvironment and boost immune responses. Chemotherapy and ICI combinations have proved successful in treating a variety of cancer types. For instance, chemotherapy (platinum-based drugs) and pembrolizumab are frequently used together as a first-line treatment in metastatic NSCLC.

**4) Additional Targeted Immunotherapies:**

Bispecific antibodies and antibody-drug conjugates can be used in combination with ICIs. These treatments may improve immune cell activation and tumor identification. For example, the combination of a bispecific T-cell engager (such as blinatumomab) and an anti-PD-1 antibody (such as pembrolizumab) has demonstrated potential in the treatment of hematologic malignancies.

**5) Oncolytic viruses:**

These viruses can target and kill cancerous cells while triggering an immune response. Oncolytic viruses and ICIs can be combined to increase immune activation and tumor cell death. These combinations are being tested in numerous clinical trials on various cancer types.

It's crucial to remember that the selection of combination therapy depends on the particular cancer kind, stage, and tumor's molecular characteristics, as well as elements specific to the patient. To improve treatment outcomes in immuno-oncology, combination treatments are continuously researched and improved. [16]

**Biomarkers in Cancer Immunotherapy:** [37]

The identification of people who are most likely to benefit from cancer immunotherapy and the evaluation of therapeutic response are both greatly aided by biomarkers. These quantifiable markers, which range from genetic and molecular traits to immune system parameters, offer important new information about the intricate relationships between tumors and the immune system. Biomarker integration in immuno-oncology has the ability to individualize treatment plans, improve patient outcomes, and get around problems like drug resistance.

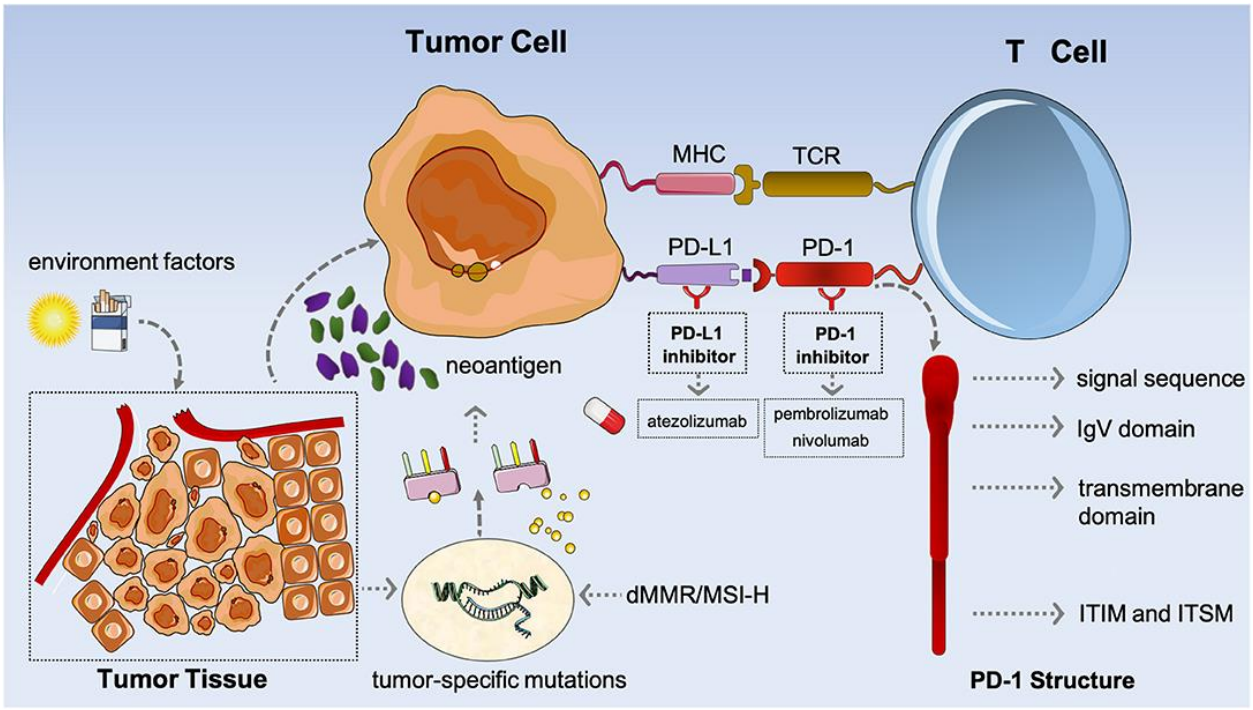


**FIG 10: The mechanism of biomarkers** [49]

**1) Predictive Biomarkers:**

Predictive biomarkers can be used to identify individuals who will likely respond favorably to immuno-oncology treatments.

- A possible predictive biomarker known as tumor mutational burden (TMB), which counts the number of genetic changes found in a tumor, has emerged.

- Across a variety of cancer types, high TMB has been linked to enhanced immune checkpoint inhibitor response rates.

- The expression of PD-L1, tumor-infiltrating lymphocytes (TILs), and the presence of particular genetic mutations or molecular fingerprints are additional prognostic biomarkers that are currently being studied.

**2) Prognostic Biomarkers:**

Prognostic biomarkers offer information concerning the general prognosis or outcome of patients receiving immuno-oncology treatment.

- A few genetic changes, including DNA mismatch repair deficiency (dMMR) and microsatellite instability (MSI), have been discovered as prognostic indicators linked to positive responses to immune checkpoint inhibitors.

- Also being investigated as prognostic indicators are immune-related gene expression profiles and immune cell infiltration patterns within the tumor microenvironment.

**3) Pharmacodynamic Biomarkers:**

These indicators measure how the immune system and the tumor microenvironment are affected by immuno-oncology therapy.

- These indicators offer insight into treatment-induced modifications to tumor features, cytokine production, and immune cell activation.

- Pharmacodynamic biomarkers can be obtained by counting immune cells and assessing their functionality, such as memory T cells or activated T cells.

**4) Monitoring Biomarkers:**

During immuno-oncology therapy, monitoring biomarkers enables the evaluation of treatment response and the detection of potential resistance mechanisms.

- Serial assessments of biomarkers, including circulating tumor DNA (ctDNA) or PD-L1 expression, can offer real-time data on the success of treatments and the development of the illness.

- Dynamic alterations in immunological biomarkers can direct modifications in the timing and length of therapy.

**5) Combination Biomarkers:** In immuno-oncology therapy, combining various biomarkers may improve their prognostic or predictive value.

- To create thorough predictive models, integrated assessments of numerous biomarkers, including both genetic as well as immune system factors, are being investigated. The goal of these combination biomarkers is to enhance patient stratification, therapy decision-making, and clinical judgment.

Precision medicine may advance with the use of biomarkers in immuno-oncology therapy, enabling individualized treatment plans and better patient outcomes. Research is still being done to test and improve biomarker-based methods, which will eventually result in more effective and individualized immuno-oncology therapies [37].

**Neoantigen Targeting: Individualised Precision** [39,40,41]

Neoantigens, distinct protein fragments resulting from mutations specific to tumours, have become intriguing targets for individualized immunotherapy. Neoantigens are excellent possibilities for precision immune targeting since these alterations only appear in cancerous cells and are missing from healthy normal cells. The identification and characterization of neoantigens have been aided by developments in genome sequencing and bioinformatics, opening the door for personalized cancer immunotherapy.

**Neoantigen Identification and Prioritisation:**

Due to the extensive mutational landscape of tumors, neoantigen identification and prioritisation provide substantial obstacles. The most immunogenic neoantigens that are most likely to trigger potent immune responses are predicted and prioritized using computational algorithms and machine learning approaches. In order to choose the best neoantigen targets, these algorithms take into account variables like mutation load, HLA binding affinity, and the presentation of antigen machinery.

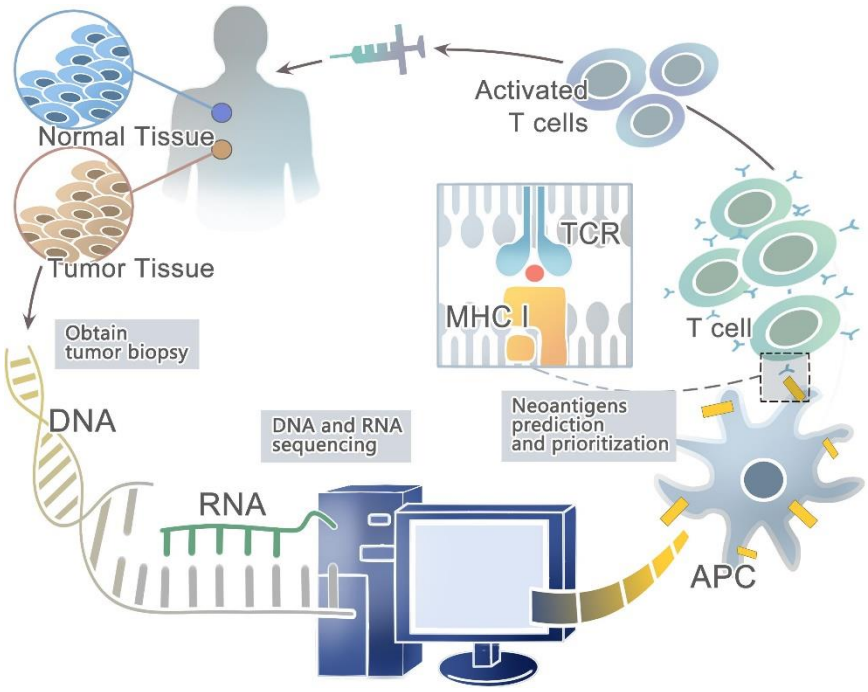


**FIG 11: Framework for the selection of important neoantigens for each cancer sample using computational analysis [50]**

**Adoptive cell therapies and individualized neoantigen vaccines:**

An innovative method in immuno-oncology is the production of personalised neoantigen vaccines and adoptive cell treatments. A patient's tumor-specific mutations are taken into account while creating a personalized neoantigen vaccine, which uses neoantigen peptides to trigger a targeted immunological response against the specific antigens found in the patient's tumour. On the other hand, adoptive cell therapies isolate and alter a patient's immune cells, including T cells, to selectively identify and eradicate cancer cells with neoantigens.

**Challenges and Future Directions in Neoantigen Targeting:**

Neoantigen targeting has a lot of potential, but it faces several obstacles before it can be widely used in medicine. The diversity of tumors, immune evasion mechanisms, and the discovery of genuinely immunogenic neoantigens are some of these difficulties. Additional challenges include the creation of scalable manufacturing methods for customised neoantigen vaccines and the improvement of adoptive cell treatments.

The development of computational algorithms to increase the precision of neoantigen prediction, the diversification of immune cells employed in adoptive cell therapies, and the investigation of combinational approaches to circumvent immunosuppressive processes are

the next directions in neoantigen targeting. Neoantigen targeting strategies may be improved by developments in gene editing tools like CRISPR-Cas9. [39,40,41]

**Approved Immuno-Oncology Drugs:** [5,16]

✓ **Approved immune checkpoint inhibitors for use in the Europe and USA are as follows:** [5]

| **Immuno-oncology drugs** | **Target** | **Type of Cancer** | **Mode of action (MOA)** |
|---|---|---|---|
| Ipilimumab (Yervoy®) | CTLA-4 | Melanoma | By inhibiting CTLA-4, we can stop the signals that suppress T cells, unleashing their potential, and leading to an immunological response against tumors. Reducing T-regulatory cells increases the ratio of active T-effector cells, causing cancer-cell-death. |
| Nivolumab (Opdivo®) | PD-1 | Melanoma, lung cancer, kidney cancer, bladder cancer, colorectal cancer, Hodgkin's lymphoma | Anti-PD-1 agents hinder the binding of PD-1 receptors to PD-L1/2 antigens found on cells within the tumor microenvironment. PD-1 serves as a suppressor of T-cell function, so inhibiting it with these agents enhances T-cell multiplication and the release of cytokines. |
| Pembrolizumab (Keytruda®) | PD-1 | Melanoma, lung cancer, head and neck cancer, gastric cancer, Hodgkin's lymphoma, MSI-high solid tumors | Similar as Nivolumab. |
| Avelumab (Bavencio®) | PD-L1 | Bladder cancer, Merkel cell cancer | By attaching to the PD-L1 antigen, it obstructs the interaction between PD-1/CD80 receptors, effectively eliminating the inhibitory impact of PD-L1 on CD8+ T cells. This enables the emergence of a potent cytotoxic T-cell response. |
| Atezolizumab (Tecentriq®) | PD-L1 | Lung cancer, bladder cancer | It directly attaches to PD-L1, resulting in a simultaneous blockade of PD-1 and CD80. This effectively eliminates the inhibitory influence of PD-L1 and PD-1 on T-cell function. |
| Durvalumab (Imfinzi®) | PD-L1 | Bladder cancer | Similar to Avelumab. |

❖ **Approved Immuno-modulatory Cytokines in the Europe and USA are as follows:** [16,42]

| Approved Cytokines | Type of Cancer |
|---|---|
| **IL-2 (aldesleukin, Proleukin®)** | Hypernephroma, Metastatic melanoma |
| **IFN-α2a (Roferon A®)** | Hairy cell leukemia, Chronic myelogenous leukemia in chronic phase with Philadelphia chromosome (Ph+ CML) |
| **IFN-α2b (Intron A®)** | Melanoma, Epidemic Kaposi's sarcoma, Hairy cell leukemia, Follicular center cell lymphoma |

**Current challenges in the field of Immuno-Oncology:** [5]

A variety of cancers have responded favourably to the development of immune checkpoint inhibitors, adoptive cell treatments, and cancer vaccines. Despite substantial progress, immuno-oncology still confronts several difficulties that limit the effectiveness and widespread use of these treatments.

**1. Tumour Heterogeneity:** Immuno-oncology faces a lot of difficulties because of tumour heterogeneity. Cancer cells have intratumoral and intertumoral heterogeneity, which promotes the growth of tumour cell clones that are resistant to treatment and escape immune monitoring. It may be possible to combat tumor heterogeneity and boost therapy response rates by designing combination medicines that target several pathways and the best biomarkers.

**2. Lack of Predictive Biomarkers:** It is still difficult to find accurate biomarkers that can predict a patient's response to immuno-oncology treatments. PD-L1 expression is now employed as a predictive biomarker for immune checkpoint inhibitors, but its usefulness has limitations, necessitating the need for additional biomarkers. To improve patient classification and treatment choice, work is being done to create novel biomarkers such as tumour mutational burden (TMB), neoantigen load, and immune gene expression profiling.

**3. Immune-related Adverse Events (irAEs):** Despite the great success of immuno-oncology therapy, irAEs are a potential side effect of these treatments. The skin, digestive system, liver, endocrine system, and other systems can all be impacted by these irAEs, which range in

severity from moderate to severe. For patients' safety and treatment continuation, it is crucial to develop methods for anticipating, managing, and reducing irAEs without sacrificing therapeutic effectiveness.

**4. Resistance Mechanisms:** Immuno-oncology medicines face a considerable obstacles from resistance. Tumour cells use several strategies, such as the suppression of antigen presentation, reduced T-cell infiltration, and stimulating immunological checkpoint pathways, to avoid immune detection. Immune checkpoint inhibitors may assist overcome resistance and improve therapy response when combined with other immunotherapeutic drugs, such as targeted treatments, cytokines, or oncolytic viruses.

**5. Cost and Availability:** Widespread acceptance and accessibility of immuno-oncology medicines are severely hampered by their high cost. These treatments are expensive in part because they frequently use intricate manufacturing procedures and tailored treatment plans. Affordability and accessibility could be improved by efforts to simplify production, cut prices, and investigate alternate therapy modalities, like off-the-shelf cell treatments.

**The Paradigm Shift in Cancer Therapy: Moving from Cytotoxicity to Immunotherapy:** [35,36]

A paradigm change in cancer therapy has occurred recently, moving away from conventional cytotoxic therapies and toward the emerging field of immunotherapy. Immunotherapy focuses on using the immune system's capacity to recognize and eliminate tumors, as opposed to cytotoxic therapies, such include chemotherapy and radiation, which try to kill cancer cells directly. This change represents a substantial improvement in the treatment of cancer and has produced encouraging results for a variety of cancer types.

Immunotherapy produces more effective, long-lasting treatment results by boosting or increasing the body's immune system's defense against cancer cells. This strategy recognizes the immune system's innate capacity to identify and get rid of aberrant cells, including cancerous cells. Immunotherapy is a potentially safer and more efficient therapeutic option compared to conventional medicines by increasing the immune system's response.

The application of checkpoint inhibitors is one of the most significant discoveries in immunotherapy. These medications target particular proteins, referred to as checkpoints that control the immune response. Checkpoint inhibitors free the immune system to more efficiently recognise and combat cancer cells by inhibiting these checkpoints. This discovery

has led to better overall survival rates and long-lasting responses in several tumours, notably melanoma, lung cancer, and bladder cancer.

The creation of adoptive cell transfer methods, such as CAR-T cell treatment, is another key development in immunotherapy. In this method, the immune cells of the patient are altered in the lab to express chimeric antigen receptors (CARs), which may identify and destroy cancer cells. Whereas conventional therapies frequently fall short in treating hematological malignancies, CAR-T cell therapy has demonstrated impressive success. Current studies are working to extend the use of CAR-T cell therapy to solid tumors, opening up new possibilities for efficient immunotherapy.

Additionally, combination medicines that include immunotherapy with conventional therapies or combine other immunotherapeutic drugs have shown considerable potential. Combination therapies strive to improve the immune response and disarm resistance mechanisms by utilizing the synergistic effects of various treatment modalities. These strategies have the potential to enhance therapeutic results and increase the number of patients who can benefit from immunotherapy.

All things considered, the transition from cytotoxicity to immunotherapy constitutes a tremendous development in the treatment of cancer. Immunotherapy has the potential to provide more precise, long-lasting, and individualized treatment choices by utilizing the immune system's innate capacity to identify and eradicate cancer cells. Immunotherapy has the ability to revolutionise cancer treatment and enhance patient outcomes on a global scale with sustained research and innovation.

**Future Prospects for Immuno-Oncology:** [36]

The development of immuno-oncology drugs has revolutionized the domain of cancer therapy and given previously untreated patients fresh hope. The management of immune-related adverse events, understanding and overcoming mechanisms of resistance, and finding prognostic biomarkers are still difficult. The goal of ongoing research is to further improve immuno-oncology strategies by combining multiple drugs, creating individualized treatments, and broadening their applications to new cancer types.

**Immuno-oncology's promising developments and ongoing innovations:** [35,36]

Immuno-oncology has emerged into a rapidly developing topic in recent years, revolutionising the landscape of cancer treatments. Researchers and doctors have made outstanding progress in creating efficient and specific cancer medicines by using the immune system to fight tumours. To highlight their transformational potential, this article examines some of the most promising recent developments and current advancements in immuno-oncology.

The creation and clinical use of checkpoint inhibitors has been one of the most important developments in immuno-oncology. These medications function by obstructing proteins like PD-1 and CTLA-4 that shield immune cells from identifying and eliminating cancer cells. Checkpoint inhibitors have demonstrated impressive effectiveness against a variety of cancers, such as melanoma, lung cancer, and bladder cancer. Patients suffering from the severe or metastatic disease now have renewed hope due to their use, which has led to long-lasting effects and increased overall survival rates.

CAR-T cell therapy is yet another ground-breaking method in immuno-oncology. In this novel therapy, immune cells from the patient are isolated, modified in the lab to produce chimeric antigen receptors (CARs), and afterward reinfused into the patient's body. These CAR-T cells that have been genetically altered are intended to recognise and destroy cancer cells only. In haematological malignancies like leukaemia and lymphoma, where conventional treatments have shown limited efficacy, CAR-T therapies have shown exceptional success. Current study presents a promising path for additional breakthroughs by extending the use of CAR-T cell treatment to solid tumours.

Researchers are investigating combination medicines that combine several immuno-oncology modalities or incorporate immunotherapies with conventional therapies including radiation therapy or chemotherapy to improve treatment outcomes. These combinations seek to improve the immune system's defense against cancerous cells and overcome the mechanisms of resistance by utilizing the complimentary modes of action. In some malignancies, for example, combining checkpoint inhibitors with targeted therapy has led to increased response rates and lengthened survival. Combination techniques show considerable potential for individualised cancer care because they enable the development of specialized regimens depending on the features of each patient and the biology of the tumor.

The creation of neoantigen vaccines is a fascinating new advance in immuno-oncology. Neoantigens are distinct protein fragments found on cancer cells that give the immune system practice in specifically identifying and attacking tumors. Neoantigen vaccines are developed to provoke an immunological reaction against these particular targets, so triggering the body's inbuilt cancer defences. This personalized technique has a lot of promise because it makes it possible to develop an immunization plan unique to a patient's tumor mutations. Neoantigen vaccines are being tested in ongoing clinical trials for their safety and effectiveness against different cancer types, opening up interesting possibilities for targeted immunotherapy.

Finally, significant developments and ongoing breakthroughs in the field of immuno oncology are still being made, and they have the potential to completely change how cancer is treated. These technological developments, which range from checkpoint inhibitors and CAR-T cell treatment to combination strategies and neoantigen vaccines, hold great promise for triggering the immunological response, engineering cellular attacks, boosting the immune system's response collaboratively, and instructing the immune system to recognize and attack tumours. Immuno-oncology is set to transform cancer treatment with additional study and advancement, bringing fresh hope to the struggle against this deadly disease.

**CONCLUSION:**

With an emphasis on the newly emerging topic of immuno-oncology, this review article work has offered an overview of the role of immunity in cancer. I explored the complex interaction between the immune system and cancer cells through an in-depth study of recent research and therapeutic developments.

The article showed that while the immune system is remarkably capable of identifying and eliminating cancer cells, tumors frequently evolve defense mechanisms to avoid immune monitoring. However, new developments in immuno-oncology have revolutionized cancer treatment by using the immune system's capacity to target and destroy tumors.

In this discussion of immuno-oncology, several different approaches, such as immune checkpoint inhibitors, adoptive cell treatments, cancer vaccines etc are covered. These novel methods have shown extraordinary clinical success, producing long-lasting effects and raising survival rates in several cancers. Additionally, we looked at how combination therapy can improve treatment outcomes.

In conclusion, this review paper has emphasized the important developments in immuno-oncology and their profound influence on cancer treatment. The entire potential of the immune system to fight cancer will only be realized with continued study, clinical trials, and collaboration among different disciplines. With continuing work, we may anticipate a time when immuno-oncology will be crucial to generating durable remissions and raising the standard of living for cancer patients.

## REFERENCES:

[1] Rang & Dale's Pharmacology, 9th Edition, Section 6, Page 82.
[2] Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. O.J.Finn. Annals of oncology, Volume 23, Supplement 8, Page viii6-viii9, September 2012. (Article).
[3] Advances in immune-oncology. Alexander Eggermont & Olivera Finn. (foreword - article).
[4] Evolution of endpoints for cancer immunotherapy trials. A.Hoos. Annals of Oncology, Volume 23, Supplement 8, Page viii47-viii52, September 2012.
[5] Sophie Carter, David E Thurston. Immuno-oncology agents for cancer therapy. May 2020. The Pharmaceutical Journal. Vol 304. No 7937, S2-S27. doi: 10.1211/PJ.2020.20207825.
[6] Roles of the immune system in cancer: from tumor initiation to metastatic progression. Hugo Gonzalez, Catharina Hagerling, Zena Werb. Page 1267-1284.
[7] The global burden of cancer 2013. JAMA Oncol. 2015 Jul;1(4):505-27. doi: 10.1001/jamaoncol.2015.0735.
[8] Asian Cancer Registry Forum 2014 - Regional Cooperation for Cancer Registration: Priorities and Challenges. Malcolm A Moore, Suleeporn Sangrajrang, Freddie Bray. March 2014. Asian Cancer Registry Forum 2014 - Regional Cooperation for Cancer Registration. Volume 15. Page 1891-1894. DOI:http://dx.doi.org/10.7314/APJCP.2014.15.5.1891.
[9] Global cancer research: Why Global Cancer Research Is Critical to Progress against the Disease.2022. National Cancer Institute. https://www.cancer.gov/research/areas/global-health
[10] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2020 (https://gco.iarc.fr/today, accessed February 2021).
[11] de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180-e190.
[12] Assessing national capacity for the prevention and control of noncommunicable diseases: report of the 2019 global survey. Geneva: World Health Organization; 2020.
[13] What is a Cancer Cell? Why does it Metastasize? Mahabaleshwar Vishnu Hegde, Aniket Vijay Mali, Shubha Sandeep Chandorkar. Asian Pacific Journal of Cancer Prevention, Vol 14, 2013. Page 3987-3989. DOI:http://dx.doi.org/10.7314/APJCP.2013.14.6.3987.
[14] Cancer: An Overview. Garima Mathur, Sumitra Nain, and Pramod Kumar Sharma. Academic Journal of Cancer Research 8 (1): 01-09, 2015. DOI: 10.5829/idosi.ajcr.2015.8.1.9336.
[15] Daniel S. Chen, Ira Mellman. Oncology meets Immunology: The Cancer-Immunity Cycle. July 2013. Elsevier Inc.
[16] Stephen Clarke, Bob T Li. Immuno-Oncology. 2017. Health Press. Page 24-26, Page 27-28 (Fig 8 & 9), Page 41, Page 44, Page 78.
[17] Understanding the Immune System: How it works. U.S. Department of Health and Human Services. National Institute of Health. National Institute of Allergy and Infectious Diseases. National Cancer Institute. NIH Publication No. 03-5423. September 2003.
[18] Cancer and the Immune system: An overview of recent publications featuring illumine technology. 17th August, 2015. Pub. No. 1170-2014-004. www.illumine.com

[19] Melissa Krystel-Whittemore, Kottarappat N. Dileepan, John G. Wood. Mast Cell: A Multi-Functional Master Cell. 06 January 2016. Volume 6. Article 620. doi: 10.3389/fimmu.2015.00620. Frontiers in Immunology | www.frontiersin.org.
[20] Eric Vivier, Elena Tomasello, Myriam Baratin, Thierry Walzer, Sophie Ugolini. Functions of natural killer cells. NATURE IMMUNOLOGY, VOLUME 9 NUMBER 5 MAY 2008. Page 503-510.
[21] Jean S. Marshall, Richard Warrington, Wade Watson, Harold L. Kim. An introduction to immunology and immunopathology. Marshall et al. Allergy Asthma Clin Immunol 2018, 14(Suppl 2):49 https://doi.org/10.1186/s13223-018-0278-1
[22] Kamta J, Chaar M, Ande A et al. Advancing cancer therapy with present and emerging immuno-oncology approaches. *Front Oncol* 2017;7:64.
[23] Messerschmidt JL, Prendergast GC, Messerschmidt GL. How cancers escape immune destruction and mechanisms of action for the new significantly active immune therapies: helping nonimmunologists decipher recent advances. *Oncologist* 2016; 21: 233–43.
[24] Ehrlich P. Über den jetzigen Stand der Karzinomforschung. *Ned Tijdschr Geneeskd* 1909;5:273−90.
[25] Thomas L. Discussion. In: *Cellular and Humoral Aspects of the Hypersensitive States*. Lawrence HS, ed. New York: Hoeber-Harper, 1959:529−32.
[26] Burnet M. Cancer – a biological approach. *Br Med J* 1957;1:779−86.
[27] Dunn GP, Bruce AT, Ikeda H, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;3:991–8.
[28] Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996;271:1734–6.
[29] Kreamer KM. Immune checkpoint blockade: a new paradigm in treating advanced cancer. *J Adv Pract Oncol* 2014;5:418–31.
[30] Wang J, Yuan R, Song W et al. PD-1, PD-L1 (B7-H1) and tumor-site immune modulation therapy: the historical perspective. *J Hematol Oncol* 2017;10:34.
[31] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011;331:1565–70.
[32] Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol* 2004;22:329–60.
[33] Herbst RS, Soria J-C, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014;515:563–7.
[34] Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol* 2016; 39 :98–106.
[35] K. Esfahani, L. Roudaia, N. Buhlaiga, S.V. Del Rincon, N. Papneja, W.H. Miller Jr. A review of cancer immunotherapy: from the past, to the present, to the future. Curr Oncol. 2020 April:27(S2)87–97. Current Oncology, Vol. 27, Supp. 2, April 2020 © 2020 Multimed Inc. S87-S97. DOI: https://doi.org/10.3747/co.27.5223
[36] Howard L. Kaufman, Michael B. Atkins, Prasun Subedi, James Wu, James Chambers, T. Joseph Mattingly, Jonathan D. Campbell, Jeff Allen, Andrea E. Ferris, Richard L. Schilsky, Daniel Danielson, J. Leonard Lichtenfeld, Linda House, Wendy K. D. Selig. The promise of Immuno-oncology: implications for defining the value of cancer treatment. Kaufman et al. Journal for ImmunoTherapy of Cancer. (2019) 7:129. Page 1-11. https://doi.org/10.1186/s40425-019-0594-0
[37] Habib Sadeghi Rad1 , Sajad Razavi Bazaz2 , James Monkman3,4 , Majid Ebrahimi Warkiani2,5 , Nima Rezaei1,6,7 , Ken O'Byrne3,4,8 & Arutha Kulasinghe3,4,9. The evolving landscape of predictive biomarkers in immuno-oncology with a focus on spatial technologies. Clinical & Translational Immunology 2020; e1215. Vol. 9. Page 1-12. doi: 10.1002/cti2.1215 www.wileyonlinelibrary.com/journal/cti
[38] Karim Pérez-Romero, Ramón M. Rodríguez, Amedeo Amedei, Gwendolyn Barceló-Coblijn and Daniel H. Lopez. Immune Landscape in Tumor Microenvironment: Implications for Biomarker Development and Immunotherapy. 2020. Page 1-14. *International Journal of Molecular Sciences.* Int. J. Mol. Sci. 2020, 21, 5521; doi:10.3390/ijms21155521 www.mdpi.com/journal/ijms

[39] Na Xie, Guobo Shen, Wei Gao, Zhao Huang, Canhua Huang, Li Fu. Neoantigens: promising targets for cancer therapy. 2023. *Signal Transduction and Targeted Therapy* (2023) 8:9; Page 1-48. https://doi.org/10.1038/s41392-022-01270-x

[40] Zheying Zhang, Manman Lu, Yu Qin, Wuji Gao, Li Tao, Wei Su, Jiateng Zhong. Neoantigen: A New Breakthrough in Tumor Immunotherapy. 2021. Article 672356. Volume 12. Front. Immunol, 16 April 2021 Sec. Cancer Immunity and Immunotherapy. https://doi.org/10.3389/fimmu.2021.672356

[41] Xuan Zhao, Xiaoxin Pan, Yi Wang, Yi Zhang. Targeting neoantigens for cancer immunotherapy. 2021. Zhao et al. Biomarker Research. (2021) 9:61. Page 1-12. https://doi.org/10.1186/s40364-021-00315-7

[42] Galluzzi L, Vacchelli E, Bravo-San Pedro JM et al. Classification of current anticancer immunotherapies. *Oncotarget* 2014;5:12472–508.

[43] Fig 1 link: https://www.freepik.com/free-vector/diagram-showing-normal-cancer-cells-human_25592420.htm

[44] Fig 4 link: https://upload.wikimedia.org/wikipedia/commons/9/97/Diagram_showing_how_cancer_cells_keep_on_reproducing_to_form_a_tumour_CRUK_127.svg

[45] Fig 2 & 3 link: https://www.healio.com/hematology-oncology/learn-immuno-oncology/the-immune-system/components-of-the-immune-system

[46] Fig 6 link: https://www.researchgate.net/journal/Journal-of-Translational-Medicine-1479-5876

[47] NAD-Biosynthetic and Consuming Enzymes as Central Players of Metabolic Regulation of Innate and Adaptive Immune Responses in Cancer - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/The-tumor-microenvironment-A-schematic-view-of-the-tumor-microenvironment-components_fig1_334688877 [accessed 8 Jun, 2023]

[48] Junaid Raja, Johannes M. Ludwig, Scott N. Gettinger, Kurt A. Schalper, Hyun S. Kim. Oncolytic virus immunotherapy: future prospects for oncology. Raja et al. Journal for ImmunoTherapy of Cancer (2018) 6:140 Page 1-13 https://doi.org/10.1186/s40425-018-0458-z

[49] Zhu Zeng, Biao Yang, Zhengyin Liao. Biomarkers in Immunotherapy-Based Precision Treatments of Digestive System Tumors. Front. Oncol., 11 March 2021. Sec. Gastrointestinal Cancers. Volume 11 – 2021. https://doi.org/10.3389/fonc.2021.650481

[50] Xue-Jiao Han, Xue-lei Ma, Li Yang, Yu-quan Wei, Yong Peng, Xia-wei Wei. Progress in Neoantigen Targeted Cancer Immunotherapies. Front. Cell Dev. Biol., 30 July 2020. Sec. Molecular and Cellular Oncology. Volume 8 – 2020. https://doi.org/10.3389/fcell.2020.00728

[51] Jean S. Marshall, Richard Warrington, Wade Watson, Harold L. Kim. An introduction to immunology and immunopathology. 2018. Marshall et al. Allergy Asthma Clin Immunol 2018, 14(Suppl 2):49. Page 5-14. https://doi.org/10.1186/s13223-018-0278-1