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Immunoncology: An Overview

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Abstract

Immuno-oncology is emerging field in which interactions of the immune system with cancer cells have been studied and find out the ways to increase or activate patient's immune system against cancer cells. Immuno-oncology approaches target only the immune system, not the malignant cells. Recently, various advancements in instruments along with computational approaches happened which increase the knowledge regarding how antigens are recognized by innate immune cells and presented to the adaptive immune system. Further knowledge about the molecules which are involved in T and B cell activation has provided new and excited immunotherapeutic strategies which can be used against the cancer cells. This chapter starts with a history of immuno-oncology along with review of the interaction of the immune system with cancer cells. Further, various approaches in immuno-oncology and the mechanism of action are presented. Finally, this chapter concludes with a summary of current challenges and future perspectives of immuno-oncology.

Keywords: Immune system; Cancer; Toll like receptor; CLT4 inhibitors; Cytokines.

Introduction

Cancer is a prominent cause of death, which is characterized by uncontrolled growth and spread of abnormal cells in the body. The exact etiology of cancer is still unknown. However, various factors play a major role in the development of various types of cancer [1]. Currently, cancer is treated by using a combination of various approaches such as surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care depending upon the type, location, and grade of cancer as well as the person's health [2]. Inspite of these approaches, the incidence of cancer keeps on increasing on a global scale. The main reason behind this is due to unavailability of safe and effective medicines in the treatment of cancer. Mostly all of the anti-cancer drugs show various side effects such as undesirable hair loss, sometimes potentially life-threatening conditions such as anemia and various infections [3]. In the present situation, there is no safe and promising cancer therapy available due to lack of knowledge of the exact mechanism of anticancer agents and their side effects. Thus, there is an urgent need for the development of new approaches in the treatment of cancer.

Immuno-oncology is an exciting new approach in the treatment of cancer. In this approach, body's own immune system is harnessed to fight against cancerous cell [4]. To fight against infectious diseases such as *polio* and *small pox*, the immune system is targeted. In a similar way, the next generation of cancer therapeutics aims to enhance the endogenous antitumor response [5]. The specificity, adaptability and memory features of immune cells indicated the tremendous potential of immune-oncological methodologies in the treatment of cancer. The immune cells have potential to detect and destroy cancer cells without affecting normal cells [6]. A summary of the various advantages of immuno-oncology has been summarized in **Table 1.**

The understanding regarding antigen recognition, presentation and the molecules involved in T and B cell activation have provided a novel and excited immunotherapeutic approaches which can be used against the cancer cells. Immuno-oncological agents do not directly attack the cancer cells but, these agents utilize the various immune response signaling pathways against cancer cells [7]. Thus, immuno-oncology drug development comprehends an extensive range of agents,

including peptides, proteins, antibodies, adjuvants, small molecules, cytokines, oncolytic viruses, bi-specific molecules and cellular remedies [8].

This chapter summarizes the history of immuno-oncology and interaction of immune system signaling pathways with cancer cells. The overview of immuno-oncology and various immuno-oncology agents along with their mechanism of action are briefly reviewed. Potential therapeutic challenges of immuno-oncology agents are also discussed. Finally, this chapter concludes with a summary of future perspectives of immuno-oncology field in treatment of cancer.

History of Immuno-Oncology

The concept of immune cell therapy for the treatment of cancer goes back to the 18th century when the possibility of using the body's immune response to help curb diseases began to be explored. Initially, it was used to control diseases other than cancer, but the idea spread to involve the world of oncology. The notion of immune cell therapy was pioneered by Dr. Steven Rosenberg (a Jewish American cancer researcher and surgeon) and his colleagues. In the late 1980s, they reported a lower tumor regression rate (2.6–3.3%) in 1205 patients with metastatic cancer who underwent different types of active specific immunotherapy. Further, James P. Allison identified cytotoxic T-lymphocyte antigen 4 or CTLA-4 in 1987. He observed that CTLA-4 prevents T cells from attacking tumor cells. He then wondered whether blocking CTLA-4 would allow the immune system to make those attacks. After continuous efforts of 9 years, he was successful to demonstrate that antibodies against CTLA-4 allowed the immune system to destroy tumors in mice. In 1999, biotech firm Medarex acquired rights to the antibody.

Later, in 2010, Bristol-Myers Squibb, who acquired Medarex in 2009, reported that antibodies have prolonged the life span by an average of 10 months (which was previously 6 months without it) in the patients suffering from metastatic melanoma [9]. This was for the first time that any treatment had prolonged life in advanced melanoma in a randomized trial. In 1997 rituximab, the first antibody treatment for cancer was approved by the FDA for treatment of follicular lymphoma [10]. Since its approval, 11 other antibodies have been approved for the treatment of cancer; alemtuzumab (2001), ofatumumab (2009) and ipilimumab (2011).

Sipuleucel-T, the first cell-based immunotherapy cancer vaccine, was approved in 2010 for the treatment of prostate cancer [11]. One PD-L1 inhibitor (atezolizumab) and two PD-1 inhibitors (nivolumab and pembrolizumab) had been approved by mid-2016 [12]. The history of FDA approved drugs for the treatment of cancer *via* immune- therapy is represented in **Figure 1**.

Cancer Cell Altered Immune Response Signaling Pathways

Cancer is one of the leading causes of death and is characterized by abnormal cell growth with a potential to invade other parts of the body. Incidences of cancer are increasing day by day due to an incomplete understanding regarding its pathogenesis. Now, oncologists started to move their focus from cancer cells to host environment in which the cancer cell grows, to increase the knowledge regarding the pathogenesis of cancer. One of the important constituents of host environment in cancer cells is immune system.

The immune system is a securely regulated and complex network which includes lymphoid, reticular, dendrite and epithelial cells. It interacts with the cell to cell contact and communicates via soluble mediators such as cytokines [13]. Generally, the immune system is divided into two parts i.e. innate immune system and adaptive immune system which works together to protect the body against any infectious agents. The innate immune system is activated whenever any infectious agents attack the body to eliminate it within hours [14]. Therefore, the innate immune system serves as the first line of defense against pathogenic organisms. Further, the adaptive immune system is activated when the innate immune system is unable to handle the pathogens. The second form of immunity, known as adaptive immunity, develops in response to infection and this type of immunity adapts to recognize, eliminate, and then to remember the invading pathogen [15].

Innate immune cells sense the pathogens by utilizing conserved receptor system of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), Nucleotide-binding oligomerization domain receptors (NOD-like receptors NLRs) and RIG-I like receptors (RLRs). These receptors are germline-encoded and do not undergo gene rearrangement due to which they are not able to distinguish small differences in pathogens [16,17]. Thus, innate immune cells are non-specific in nature and are not able to recognize a large number of diverse antigens. The large numbers of antigens are recognized by T cell receptors and immunoglobulins of T & B cells respectively which are generated by gene arrangement.

The innate responses use phagocytic cells (neutrophils, monocytes and macrophages), cells that release inflammatory mediators (basophils, mast cells and eosinophils) and natural killer cells for the destruction of pathogens. The molecular components of innate responses include complement, acute phase protein, and cytokines such as interferons. The adaptive immune system uses specific B & T cells, which are generated in the lymph nodes, spleen and mucosa-associated lymphoid tissue (MALT). Antigen-presenting cells (APC) display the processed antigen to the lymphocyte which leads to activation of various adaptive immune response signaling pathways [18].

The adaptive immunity is a pathogen-specific host defense based on clonally expanded B and T lymphocytes generated first through random somatic recombination of immunoglobulin genes and then through positive and negative selections. These pathogens-specific B and T lymphocytes not only serve as effector cells for pathogen eradication, but they also function as memory cells for rapid expansion upon re-encountering these pathogens. The adaptive immunity is highly specific and effective against evolving pathogens and takes days or weeks to develop.

Cell surface receptors receive the initial signals that activate complex immune responses. In case of innate immunity, the signal will be a microbial product, the receptor will be PRR on a leukocyte and the signal will be transduced by the interaction of specific intracellular molecules results in the clearance of the invading organism. In case of adaptive immunity, the signal will be processed MHC antigenic peptide complexes on APCs [19]. This event catalyzes a series of intracellular events resulting in the transcription of genes that drive the differentiation of the T cell. Innate and adaptive responses usually work together to eliminate pathogen [20].

Cancer arises from the accumulation of at least one, and typically multiple, mutations, which then translate into changes in the structure of key proteins. These changed structures of proteins are much like viral proteins that are recognized as foreign materials by the immune system [21]. Thus, the question arises why don't these mutated tumors, which are now at least partially foreign, are not destructed by the immune system? This may happen due to the origin of cancer cells from our own cells due to which immune system is unable to detect these cells as non-self. In some cases, the immune system is able to detect these cells but unable to activate further immune signaling pathways by inhibiting various steps.

The cancer cells can avoid recognition and elimination by altering the immune response signaling pathways at various steps such as disrupting antigen recognition and presentation mechanisms, downregulates the MHC class I molecules or inhibiting the antigen processing mechanisms [22]. Additionally, cancer cells may disrupt the pathways which are involved in controlling T-cell inhibition and activation, or by recruiting regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) which are immunosuppressive [23]. Further, cancer cells may release of some of the immunosuppressive immune factors such as adenosine and prostaglandin E2, and the enzyme indoleamine 2,3-dioxygenase (IDO) which leads to progression of cancer [24].

Disrupting Innate Immune Response Signalling Pathways

Normally, antigens are recognized by immune system through sensors such as Toll-like receptors (TLRs). Toll-like receptors are transmembrane proteins that detect invading pathogens by binding conserved, microbially derived molecules and that induce signaling cascades for pro-inflammatory gene expression [25]. TLRs are widely expressed in many cell types such as macrophages, neutrophils, and dendritic cells. Thus far, 13 mammalian TLRs, 10 in humans and 13 in mice, have been identified. TLRs 1–9 are conserved between humans and mice, yet TLR10 is present only in humans and TLR11 is functional only in mice. The biological roles of TLRs 10, 12, and 13 remain unclear, as their expression patterns, ligands, and modes of signaling have yet to be defined. Among the characterized TLRs, TLR1, 2, 4, 5 and 6 are represented on the cell surface and seem to specifically recognize bacterial and fungal products that are not made by the host, whereas TLR3, 7, 8 and 9 reside in intracellular endosomes and specialize in the detection of nucleic acids of pathogens [26]. For example, lipopolysaccharide (LPS), a common structure of the cell wall of Gram-negative bacteria, is recognized by TLR4; double-stranded RNA (dsRNA), which has long been considered a viral PAMP, triggers TLR3 signaling pathways.

Toll-like receptor (TLR) activate MyD88-dependent and independent signaling pathways that lead to activation of transcription factors nuclear factor-κB (NF-κB), interferon regulatory factor 3/7 (IRF3/7) and/or activator protein-1 (AP-1), which collaborate to induce transcription of a large number of downstream genes [27].

MyD88-Dependent Signaling

In normal condition, the exogenous or altered cells bind with the extracellular portion of the TLR as shown in **Figure 2.** On the cytoplasmic side, adaptor protein (MyD88) interact with the TIR domain of TLRs. Adaptor protein promotes the as-

sociation of two protein kinases, IRAK1 and 1RAK4. The protein kinase IRAK4, of the IRAK1:IRAK4 complex phosphorylates its partner, IRAK1 and provides the docking site for TRAF6, which binds and form a complex resulting in the activation of the TAK1 kinase activity. TAK1 activates mitogen-activated protein kinase (MAP kinase) pathway and NFkβ pathway [28].

MAP kinase pathway

Mitogen activated protein (MAP) kinases are a group of highly conserved serine/ threonine protein kinases which are present in eukaryotes [25]. These proteins play pivotal roles in a variety of cellular processes including proliferation, differentiation, stress response, apoptosis, and host immune defense. In innate immune cells, MAP kinases are critical for the syntheses of numerous cytokines, chemokines, and other inflammatory mediators that mobilize the immune system to combat pathogenic infections. The activated MAP kinases can translocate to the nucleus and phosphorylate proteins that control chromatin structure as well as numerous transcription factors such as AP-1, thereby influencing the transcription of MAP kinase-regulated genes [29].

NFkβ pathway

The nuclear factor-kB (NF-kB) family of transcription factors encompasses a collection of structurally related proteins that modulate numerous physiological processes, ranging from immune responses to cell death and survival. The eukaryotic NF-κB transcription factor family controls the expression of a large variety of genes that are involved in a number of processes like inflammatory and immune responses of the cell, cell growth, and development [30]. NF-κB transcription factors are triggered as a response to a variety of signals, including cytokines, pathogens, injuries, and other stressful conditions. Activation of NF-κB proteins is tightly controlled, and inappropriate activation of the NF-κB signaling pathways has been related to autoimmunity, chronic inflammation, and various cancers. In normal cells, IκB (inhibitory cells) binds to NF-κB&sequesters this complex in the cytoplasm which ultimately prevents the binding of NF-κB with DNA. This process leads to inhibition of immune response signaling pathways.

When immune cells sense foreign cells or altered cells of the body, the signal is transmitted into the cell and adaptor signaling proteins initiate various signaling cascades. These signaling cascades activates IκB kinases (IKK) which phosphorylates the inhibitory complex (NF-κB•IκB). The free NF-κB proteins are transported into the nucleus and bind to the target sequence which results in gene transcription [31]. In innate immune response, these transcription results in the formation of various cytokines such TNF-α, IL-I etc. The NF-κB also has a central function in the adaptive immune response.

MyD88-Independent/TRIF Dependent Signaling

Toll like receptors (TLR4 and TLR3) stimulation result in the MyD88-independent activation of IRF3, a key transcription factor necessary for IFNß production and the delayed-phase NFκB activation via TLR4 [32]. Although, it has been studied extensively but the mechanism by which TRIF activates NFκB and IRF3 is still unclear. The N terminus of TRIF is believed to form a complex with TBK-1, IRF3, and possibly IKKi for the specific phosphorylation and activation of IRF3. Type I IFNs (IFN-a/ß) are integral components of innate antiviral responses, and their expression is governed by IRF transcription factors. Two members of this family, IRF3, and IRF7, are absolutely required for transcription of IFN-a/ß genes [33]. Upon viral infection, latent IRF3 is phosphorylated at C-terminal serine residues, which leads to its dimerization and subsequent translocation to the nucleus. Upon entering the nucleus, IRF3 synergizes with co-activator molecules and binds DNA elements at the IFN-ß promoter to induce gene transcription. In contrast, IRF7 is basally present only in plasmacytoid dendritic cells, which are specifically adapted to detect viruses and synthesize IFNα upon infection, but is strongly induced in many cells after a viral infection and subsequent type I IFN autocrine/paracrine signalling.

Cancer cells which arise from normal cells are difficult to be recognized by TLRs as presented in **Figure 2**. If they are not recognized, further TLR signaling pathways will not be activated. In some cases, these cells are recognized by innate immune cells but inhibit signaling pathways. How cancer cells inhibit TLR response signaling pathways is still an open question for researchers and needs to be answered.

Disrupting antigen presentation mechanisms

In normal conditions, the processed antigen is presented to T-cell for destruction but unfortunately, cancer cells alter their presenting mechanism and lead to adaptive immune system failure.

Dendiritic cells act as antigenic presenting cell (APC). The antigen is processed intracellularly into short peptides by means of proteolytic cleavage before it is presented by major-histocompatibility-complex (MHC) molecules on the surface of

dendritic cells.

At least two signals are required for the activation of T-cell. The first signal is generated by MHC-Peptide complex and another from co-stimulatory molecules i.e. B7 [34, 35, 36]. Co-stimulatory molecules are molecules that provide the signals necessary for lymphocyte activation in addition to those provided through the antigen receptor. CD80 & CD86 belongs to B7 family and is extensively studied in labs for their interaction with CD28 & CLTA-4 (cytotoxic T-lymphocyte-associated antigen-4) [37, 38]. CD28 is expressed on human & murine T-cells and upon ligation with CD80 & CD86 leads to activation of co-stimulatory signals. The pictorial representation of the mechanism is shown in **Figure 3**.

Disrupting cytokines release

Normally, when the antigen is presented to T-cell, naïve CD4+ T-cells will become active & attain effector functions by differentiating into T-helper (Th) subsets. These subsets are distinguished as Th1 and Th2 T cells, and they are categorized by their varying ability to produce cytokines and to express surface receptors [39]. It can take several rounds of activation for T cells to differentiate terminally to either Th1 or Th2, which suggests that T cells can be activated and expanded in a non-polarized manner.

Cancer cells alter the antigen presenting and activation mechanism which ultimately results in the decreased release of cytokines specifically which is released from helper and cytotoxic T cell for the destruction of exogenous agents [40] as presented in **Figure 4**.

Immuno-oncology

Immuno-oncology is made up of two words i.e. immune & oncology which mean the study of the immune system in cancer environment [41]. Recently, this field has aroused the attention of researcher to use immune cells for treatment of cancer. This field is still evolving and have potential to provide new therapeutic agent against cancer. To understand immune response signaling pathways, research is in a continuous process and recently various mechanisms of these pathways have been explored which will be helpful for providing new agents. Current approaches are based on agents that can break immune tolerance. Presently, numbers of immunotherapies having different mechanisms for cancer patients are under clinical trials [42].

Immuno-oncological approaches

Firstly, cancer cells should be detected by immune system by sensors such as Toll Like receptors, NOD like receptors etc. Thus, currently various approaches are under investigation to increase the recognition power of immune system against cancer cells. Secondly, in normal response, the activated immune response signalling pathways should be deactivated to prevent self destruction to the host cells. The numerous immune checkpoint pathways control activation of T cells at multiple stages during an immune response, a process called peripheral tolerance. Central to this process is the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) immune checkpoint pathways. The CTLA-4 and PD-1 pathways are thought to operate at different stages of an immune response [37]. CTLA-4 is considered the "leader" of the immune checkpoint inhibitors, as it stops potentially autoreactive T cells at the initial stage of naive T-cell activation, typically in lymph nodes. The PD-1 pathway regulates previously activated T cells at the later stages of an immune response, primarily in peripheral tissues [38]. Cancer cell induces immune-suppressive effect by taking advantages of these pathways as shown in **Figure 3**. The various immune-oncological approaches are described below.

Toll-like receptors (TLRs) agonists

Toll-like receptors (TLRs), recognize the conserved molecular structures found in pathogens called pathogen-associated molecular patterns (PAMPs) which leads to the activation of innate immune signaling pathways [43]. Members of TLRs are well conserved in both human and mouse, consisting of at least 11 members. The agonists of toll-like receptors (TLRs) have been actively pursued their anticancer potentials, either as monotherapy or as adjuvants to vaccination or other therapeutic modalities [44]. The bacillus Calmette-Guérin (BCG, an attenuated strain of Mycobacterium bovis initially developed as an anti-tuberculosis vaccine), have been shown to potently activate TLR2 and TLR4 and approved by the FDA for bladder carcinoma [45]. Similarly, Imiquimod (a small Imidazoquinoline that was originally developed as a topical antiviral agent) act as TLR7 agonist and approved by the FDA for superficial basal cell carcinoma. Further, TLR9 agonists are under clinical development phase which directly induce activation and maturation of plasmacytoid dendritic cells and enhance differentiation of B cells into antibody-secreting plasma cells. The immune role of TLR9 has been studied most extensively in

plasmacytoid dendritic cells (pDCs) and B cells, which may be the only human immune cells to constitutively express TLR9.

Checkpoint inhibitors

The checkpoint inhibitors are another class of immunological agents which stimulates or switch off T cell activity to show their anti-cancer activity. These agents have more potential as anti-cancer agents specifically in the treatment of advanced stage of cancer. The first immunotherapy as the CLT4 inhibitor, which is approved for treatment of cancer as checkpoint inhibitor, is ipilimumab which blocks cytotoxic T lymphocyte-associated antigen 4 (CLTA 4) [46, 47]. Other checkpoint inhibitors for the treatment of cancer that blocks programmed cell death receptors or its ligand are under various phases of clinical trials.

Cytokines therapy

Cytokines have the capacity to stimulate an immune response by activating T cells development and their differentiation into the effector cells [48, 49]. Interleukin-2 (IL-2), a cytokine that stimulates the growth, differentiation, and survival of antigen-selected cytotoxic T cells, resulted in durable anticancer responses. In 1992, FDA has approved IL-2 in the treatment of metastatic renal carcinoma. IL21 and IL7 are other types of cytokines which are under clinical development phase along with a combination of other drugs for the treatment of cancer.

Cancer Vaccines

Cancer vaccines are also one of the promising approaches in the field of immuno-oncology for the treatment of cancer. These are designed to eradicate cancer cells through strengthening patient's own immune responses against cancer cells. The various immune effector mechanisms mobilized by therapeutic vaccination specifically attack and destroy cancer cells and spare normal cells [50]. These vaccines are prepared by using various approaches such asa combination of tumor cells with immunostimulatory adjuvants and these are administered to the individual from whom the tumor cells were isolated. The approval of sipuleucel-T (a therapeutic vaccine composed of recombinant antigen protein) was designed to stimulate T-cell responses. [51, 52]. The various vaccines which are under various phases of clinical trials are summarized in **Table 2**.

Currently FDA approved and under clinical trials Immuno-oncological drugs

Currently, the FDA has approved ipilimumab and pembrolizumab for their use as a prescription drug as summarized in **Table 3** [53]. Apart from this, some drugs are under various phases of clinical trials for the treatment of cancer, which are summarized in **Table 4**.

Current Challenges and Future Perspectives

Immuno-oncology is a promising field in the treatment of cancer by which quality of life of cancer patients could be improved by treating various immune response signaling pathways. However, there are various questions which are yet to be answered such as how to use these new immunotherapies most effectively to achieve the best possible patient outcomes. Can we combine immunotherapies that target distinct immune pathways? Can we combine immunotherapeutic agent with existing treatment modalities such as radiotherapy, chemotherapy? What is the optimal dose, schedule of therapies in combination regimens? These are some important questions which have to be answered. At present, it is difficult to identify the best combination approaches, sometimes combinations lead to the unexpected toxicity (e.g. ipilimumab and vemurafenib). Thus, there is a need for more preclinical and clinical studies which will help to direct immuno-oncology research.

Conclusion

The development of new immunotherapies against various diseases is based upon many years of researcher's hard work to understand the complex signaling pathways of immune systems. As that knowledge increases, researchers will hold the keys to developing new treatments that have the potential to change the ways in which we treat cancer. However, there is a number of questions which are unanswered regarding immuno-oncology but we hope, in future, immuno-oncology will answer most of the question and benefit a large number of cancer patients with minimum side effects.

Acknowledgment

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Figures

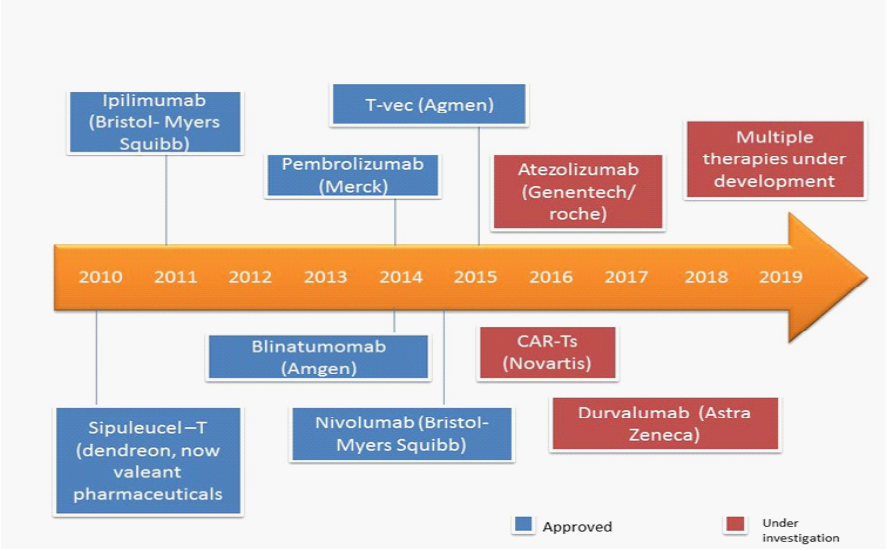

Figure 1: History of FDA approved drugs for the treatment of cancer via immune- therapy.

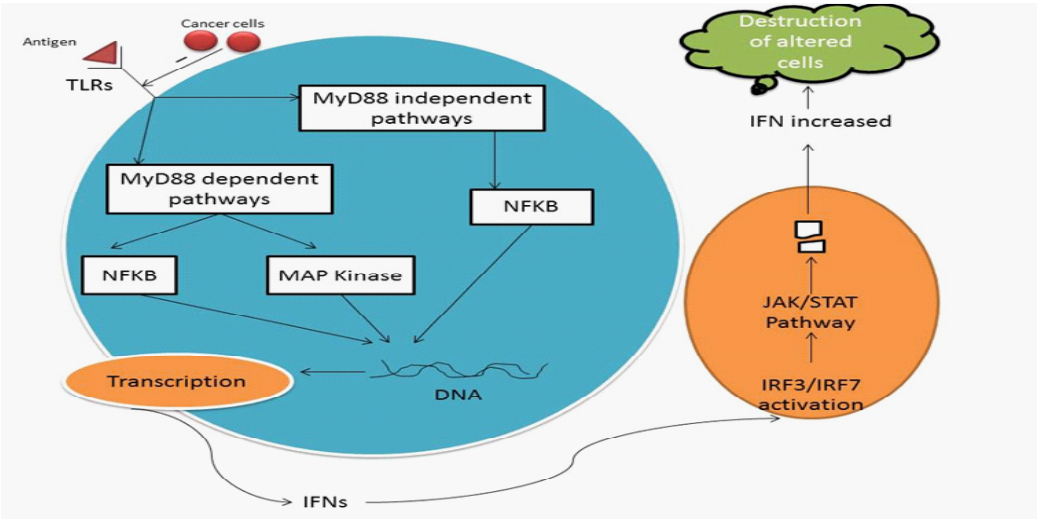

Figure 2: Cancer cell altered toll like receptor signaling pathways.

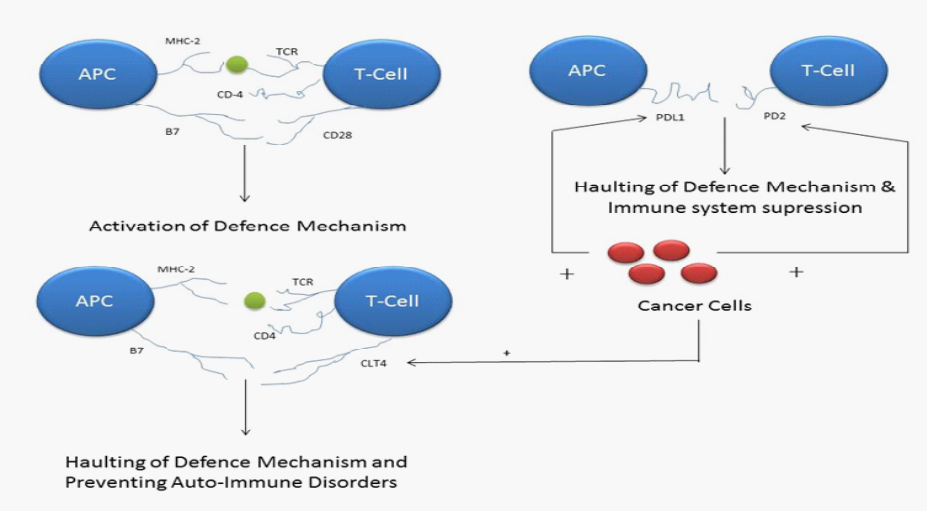

Figure 3: Cancer cell altered antigen presenting mechanism

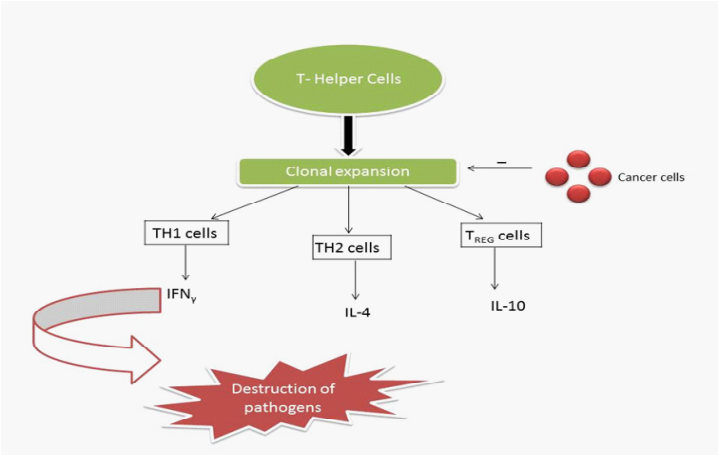

Figure 4: Cancer cell altered cytokine release pathways

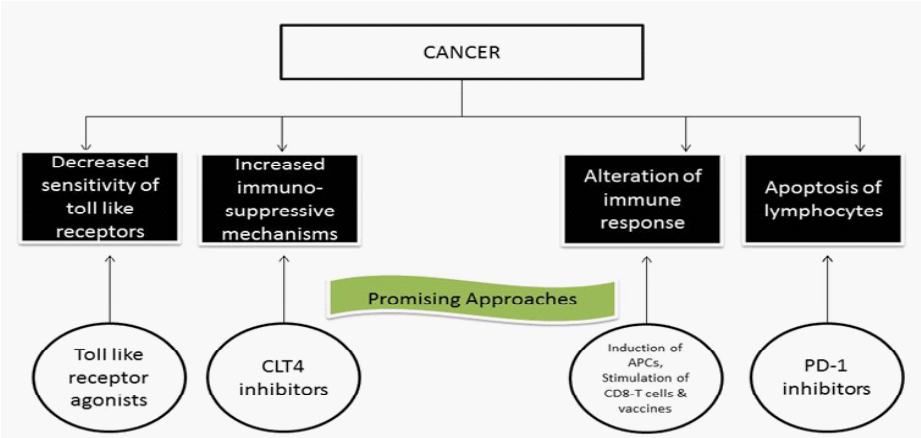

Figure 5: Promising immunooncological approaches in treatment of cancer.

Tables

Table 1: Advantages of Immuno-oncological approaches

•	Therapies lasts for a long time
•	Trains the immune system to fight against cancer cells even after remission, by generating memory cells.
•	Offers hope of long term, quality survival for the first time to many patients for whom prognosis was previously very poor.
•	Side effects are manageable as compared to other therapies

Table 2: Various vaccines which are under various phases of clinical trials

Sr. No	Study title	Conditions	Interventions	Phase
1.	Cancer vaccine study for unresectable stage III non-small cell lung cancer (START)	Follicular lymphoma	Biological: Tecemotide (L-BLP25) Drug: Single low dose cyclophos-phamide Drug: Placebo	Phase III
2.	Ovarian cancer vaccine for patients in remission	Epithelial ovarian cancer	Biological: Cvac	Phase II
3.	Tecomotide (L-BLP25) in rectal cancer	Rectal cancer	Biological: Tecemotide (L-BLP25) Drug: cyclophosphamide (CPA) Other: Chemoradiotherapy	Phase II
5.	Phase II Feasibility Study of Dendritic Cell Vaccination for Newly Diagnosed Glioblas-toma Multiforme	Glioblastoma Multiforme	Biological: Autologous Dendritic Cell Drug: Temozolomide Procedure: Radiotherapy Biological: Dendritic Cell Vaccine	Phase II

6.	Sequencing of Sipuleucel-T and ADT in Men with Non-metastatic Prostate Cancer	Prostatic Neoplasm, Prostate Cancer, Prostatic Adenocarcinoma	Biological: sipuleucel-T Drug: leuprolide acetate	Phase II
7.	A Pilot Study of Autologous T-Cell Transplantation with Vaccine Driven Expansion of Anti-Tumor Effectors After Cytoreductive Therapy in Metastatic Pediatric Sarcoma	Ewing's Sarcoma, Rhabdomyosarcoma	Biological: therapeutic autologous dendritic cells Drug: indinavir sulphate Procedure: peripheral blood stem cell transplantation	Phase II
8.	Concurrent vs. Sequential Sipuleucel-T & Abiraterone Treatment in Men with Metastatic Castrate Resistant Prostate Cancer	Prostate Cancer Metastatic, Hormone Refractory Prostate Cancer, Castration-resistant Prostate Cancer	Biological: sipuleucel-T Drug: abiraterone acetate	Phase II
9.	Open Label Study of Sipuleucel-T in Metastatic Prostate Cancer	Prostate cancer	Biological: sipuleucel-T	Phase II
10.	Study of NY-ESO-1 ISCOMATRIX® in Patients With Measurable Stage III or IV Melanoma	Melanoma	Biological: NY-ESO-1 ISCOMATRIX® vaccine Drug: Cyclophosphamide	Phase II
11.	To Evaluate Sipuleucel-T Manufactured With Different Concentrations of (PA2024) Antigen	Prostate cancer	Biological: sipuleucel-T	Phase II
12.	Sipuleucel-T Manufacturing Demonstration Study	Cancer of the Prostate, Neoplasms	Biological: sipuleucel-T	Phase II
13.	Vaccine Therapy in Treating Patients With Ovarian Epithelial or Primary Peritoneal Cancer	Ovarian Cancer, Primary Peritoneal Cavity Cancer	Biological: incomplete Freund's adjuvant Biological: ovarian cancer peptide vaccine Biological: sargramostim Biological: tetanus toxoid helper peptide Procedure: adjuvant therapy	Phase I
14.	Vaccine Therapy in Treating Patients With Stage I, Stage II, or Stage III Non-small Cell Lung Cancer	Lung Cancer	Biological: autologous dendritic cell cancer vaccine	Phase II
15.	153Sm-EDTMP With or Without a PSA/TRICOM Vaccine To Treat Men With Androgen-Insensitive Prostate Cancer	Prostate Cancer	Radiation: Samarium Sm 153 lexidronam pentasodium Biological: Sargramostim Biological: Recombinant vaccinia-TRICOM vaccine Biological: Recombinant fowlpox-TRICOM vaccine	Phase II
16.	Vaccine Therapy in Treating Patients at High Risk for Breast Cancer Recurrence	Breast Cancer	Biological: Globo-H-GM2-Lewis-y-MUC1-32(aa)-sTn(c)-TF(c)-Tn(c)-KLH conjugate vaccine Biological: QS21	--
17.	Vaccine Therapy in Treating Patients With Stage III or Stage IV Breast Cancer	Breast Cancer	Biological: synthetic breast cancer peptides-tetanus toxoid-Montanide ISA-51 vaccine	Phase I
18.	Immunogenicity of Fluzone HD,A High Dose Influenza Vaccine, In Children With Cancer or HIV	HIV Cancer	Biological: Fluzone High Dose Vaccine Biological: Fluzone Standard Dose Vaccine	Phase II

19.	Vaccine To Prevent Cervical Intraepithelial Neoplasia or Cervical Cancer in Younger Healthy Participants	Cervical Cancer Precancerous Condition	Biological: human papillomavirus 16/18 L1 virus-like particle/AS04 vaccine Biological: hepatitis A inactivated virus vaccine	Phase III
20.	Study Comparing High-Dose Flu Vaccine to Standard Vaccine in Cancer Patients Less Than 65 Receiving Chemotherapy (IMMUNE)	**Cancer** Influenza Viral Infections	Biological: Standard Trivalent Influenza Vaccine Biological: High-Dose Influenza Vaccine	Phase II
21.	Prospective Trial of Vaccine Responses Against Pneumococcus and Influenza in Adult Cancer Patients 65 Years of Age and Older	Breast Cancer Lung Cancer Prostate Cancer	Biological: inactivated influenza vaccine and the 23- valent pneumococcal vaccine Biological: inactivated influenza vaccine and the PPV23 vaccine (Pneumovax)	Phase II
22.	DC Vaccine Combined With IL-2 and IFNα-2a in Treating Patients With mRCC	Kidney Cancer	Biological: Aldesleukin,Biological: autologous tumor cell vaccineBiological: recombinant interferon alfa	Phase II
23.	Sequential Vaccinations in Prostate Cancer Patienta	Prostatic Neoplasms	Drug: Recombinant Fowlpox-GM-CSF Drug: Recombinant Fowlpox-PSA (L155)-TRICOM (PROSTVAC-F/TRICOM) Drug: Recombinant Vaccinia-PSA (L155)-TRICOM (PROSTVAC-V/TRICOM) Drug: Recombinant Human GM-CSF	Phase I Phase II
24.	OPT-821 With or Without Vaccine Therapy in Treating Patients With Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Peritoneal Cancerin Second or Third Complete Remission	Ovarian and fallopian tube cancer	Other: Laboratory Biomarker Analysis Biological: Polyvalent Antigen-KLH Conjugate Vaccine Biological: Saponin-based Immunoadjuvant OBI-821	Phase II
25.	Men's Beliefs About Associations Between HPV, Cancers, and HPV Vaccination	Anus neoplasms	--	--
26.	Study of the MUC1 Peptide-Poly-ICLC Adjuvant Vaccine in Individuals With Advanced Colorectal Adenoma	Risk for Colorectal Cancer	Biological: MUC1 - Poly ICLC	Phase II
27.	Vaccine Therapy and GM-CSF in Treating Patients With Acute Myeloid Leukemia, Myelodysplastic Syndromes, Non-Small Cell Lung Cancer, or Mesothelioma	Leukemia, Lung Cancer, Malignant Mesothelioma, Myelodysplastic Syndromes, Primary Peritoneal Cavity Cancer	Biological: WT-1 analog peptide vaccine Biological: incomplete Freund's adjuvant Biological: sargramostim Genetic: polymerase chain reaction Other: flow cytometry Other: immunoenzyme technique	Phase I
28.	Docetaxel Alone or in Combination With Vaccine to Treat Breast Cancer	Breast Cancer	Drug: Docetaxel Biological: PANVAC-V Biological: PANVAC-F Biological: Sargramostim	Phase II

29.	Vaccine Therapy in Treating Patients With Newly Diagnosed Glioblastoma Multiforme (ACTIVATe)	Malignant Neoplasms of Brain	Biological: PEP-3 vaccine Biological: sargramostim Drug: Temozolomide	Phase II
30.	Ipilimumab +/- Vaccine Therapy in Treating Patients With Locally Advanced, Unresectable or Metastatic Pancreatic Cancer	Pancreatic Cancer	Drug: Ipilimumab Biological: Pancreatic Cancer Vaccine	Phase I
31.	Dendritic Cell Vaccine Study (DC/PC3) for Prostate Cancer	Prostate Cancer	Biological: autologous dendritic cell vaccine (DC/PC3)	Phase I Phase II
32.	A Phase 1 Study of Mixed Bacteria Vaccine (MBV) in Patients With Tumors Expressing NY-ESO-1 Antigen	Melanoma, Sarcoma, Gastrointestinal Stromal Tumor (GIST), Head and Neck Cancer, Transitional Cell Carcinoma, Prostate Cancer, Ovarian Carcinoma, Esophageal Cancer, Breast Cancer	Biological: Mixed bacterial vaccine	Phase I
33.	An Intervention Study To Improve Human Papilloma-Virus (HPV) Immunization in Haitian and African American Girls (HPV)	Cervical cancer	Behavioral: BNI-brief Negotiated Interview	--
34.	Vaccine Therapy Combined With Adjuvant Chemoradiotherapy in Treating Patients With Resected Stage I or Stage II Adenocarcinoma (Cancer) of the Pancreas	Pancreatic cancer	Biological: GVAX pancreatic cancer vaccine	Phase II
35.	Vaccine Therapy, Cyclophosphamide, and Cetuximab in Treating Patients With Metastatic or Locally Advanced Pancreatic Cancer	Pancreatic cancer	Drug: Cetuximab Biological: Pancreatic tumor vaccine Drug: Cyclophosphamide	Phase II
36.	Radiation, Chemotherapy, Vaccine and Anti-MART-1 and Anti-gp100 Cells for Patients With Metastatic Melanoma	Melanoma Skin Cancer	Drug: MART-1: 26-35(27L) Peptide Drug: Montanide ISA 51 VG Drug: gp100:154-162 Peptide Procedure: Radiation Drug: Aldesleukin Drug: Fludarabine Drug: Cyclophosphamide Genetic: Anti-gp 100:154 TCR PBL Genetic: Anti-MART-1 F5 TCR PBL	Phase II
37.	Safety and Effectiveness of a Vaccine for Prostate Cancer That Uses Each Patients' Own Immune Cells.	Prostate cancer	Biological: vaccine vehicle only Biological: DC/LNCaP	Phase I Phase II

38.	Pilot Trial of a WT-1 Analog Peptide Vaccine in Patients With Myeloid Neoplasms	Leukemia	Biological: WT-1 Drug: Montanide Drug: Sargramostim (GM-CSF)	--
39.	A Study of V503, a 9-valent Human Papillomavirus (9vHPV) Vaccine in Females 12-26 Years of Age Who Have Previously Received GARDASIL™ (V503-006)	Cervical Cancers, Vulvar Cancers, Vaginal Cancers, Genital Warts	Biological: V503 Biological: Placebo to V503	Phase III
40.	Vaccine Therapy in Treating Patients With Liver or Lung Metastases From Colorectal Cancer	Colorectal Cancer Metastatic Cancer	Biological: falimarev Biological: inalimarev Biological: sargramostim Biological: therapeutic autologous dendritic cells	Phase II
41.	Study of an Investigational Vaccine in Pre-Adolescents and Adolescents (Gardasil) (V501-016)	Cervical Cancer Genital Warts	Biological: V501, Gardasil, human papillomavirus (type 6, 11, 16, 18) recombinant vaccine	Phase III
42.	Evaluation of Safety of a Vaccine Against Cervical Cancer in Healthy Korean Females	Infections, Papillomavirus	Biological: Cervarix. Other: Data collection	--
43.	V501 Safety and Efficacy Study in Japanese Women Aged 16 to 26 Years (V501-110)	Cervical Cancer, Cervical Intraepithelial Neoplasia, Adenocarcinoma in Situ	Biological: V501	Phase III
44.	HPV Vaccination: An Investigation of Physician Reminders and Recommendation Scripts	Human Papilloma Virus Infection Type 11, Human Papilloma Virus Infection Type 16, Human Papilloma Virus Infection Type 18, Human Papilloma Virus Infection Type 6, Cervical Cancer, Genital Warts, Oropharyngeal Cancer	Behavioral: Automated Reminder Behavioral: Automated Reminder Plus Script	--
45.	Wilm's Tumor 1 Protein Vaccine to Treat Cancers of the Blood	Leukemia, Myelodysplastic Syndrome (MDS), Non-Hodgkin's Lymphoma (NHL)	Drug: WT1 Peptide-Pulsed Dendritic Cells Drug: Donor Lymphocytes Drug: IL-4 Drug: KLH Drug: WT1 Peptides Drug: Endotoxin Drug: Diphenhydramine Drug: Acetaminophen	Phase I Phase II

Table 3: FDA Approved Immuno-oncological drugs

Drug Name	Active Ingredients	Strength	Dosage form; Route	Marketing status
YERVOY	Ipilimumab	3mg	Injectable; Injection	Prescription
KEYTRUDA	Pembrolizumab	50mg	Powder; For Injection Solution; Lyophilised Powder	Prescription

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