**Cancer Immunotherapy –a propitious genesis in cancer indagation**

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**ABSTRACT**

One of the most important developments in oncology in recent years is cancer immunotherapy. After decades of unsatisfactory results, immune therapy has finally turned the tide and is now a clinically proven treatment for many malignancies. Various Immune therapies have demonstrated remarkable success over the past few decades and have been approved for the treatment of different cancer therapies. While the recent development of immunotherapy with checkpoint inhibitors has drastically altered the approach to treating various cancers due to the significant survival advantages. However patient responses to immunotherapies are variable and approximately 50% of cases are refractory to these agents. Additionally, immunotherapy develops become a busy area of study in both the oncology and cancer biology fields. This article makes conceptual and historical review which summarizes the main advances in our understanding of the role of the immune system in cancer immune therapy and emerging data for the treatment of triple negative breast cancer, gastric cancer, hepatobiliary cancer, while describing the methodological details that have been successfully implemented in cancer treatments and that may hold the key to improve therapeutic approaches .Furthermore the current development in nanotechnology based cancer immunotherapy have been presented and discussed.

**Keywords:** Cancer immunotherapy triple negative breast cancer, gastric cancer, hepatobiliary cancer, nanotechnology.

**I. INTRODUCTION**

In the late 19th century, William B. Coley, commonly known as the "Father of Immunotherapy," proposed the idea of using the immune system's capacity to fight cancer. In 1891, Coley's trials involving the injection of live S. pyogenes and S. marcescens bacteria (also known as Coley's toxin) into cancer patients who were unable to undergo surgery produced encouraging results [3,4,5]. Following this, Thomas and Macfarlane's conceptualization of the "cancer immune surveillance" hypothesis and Paul Ehrlich's 1909 theory that the body continuously produces transformed cells that are eliminated by the immune system laid the foundation for later understanding of cancer immunology[6]. A new paradigm in cancer treatment has emerged as a result of our growing understanding of immune surveillance and editing processes. In addition to influencing tumor immunogenicity, the immune system also plays a dual role in preventing tumor growth by activating innate and adaptive immune systems [7]. Since the previous two decades, there has been a significant advancement in our knowledge of how cancers affect the immune system, which has led to the creation of ground-breaking therapies that stop tumor immune evasion. It was Allison and Honjo's discovery of the T-cell immune checkpoints CTLA-4 and PD-1 that launched the study of cancer immunology into the current era of cancer immunotherapy and earned them the Nobel Prize in Physiology or Medicine in 2018[8]. Despite advances in the development of anticancer medications and treatments, cancer still has the greatest fatality rate due to its dismal prognosis. Examples of conventional cancer therapies include chemotherapy, radiation therapy, and targeted therapy. The limitations of conventional medicines include lack of selectivity, non-specific cytotoxicity, inadequate drug delivery to cancer locations, and multi-drug resistance, all of which result in less effective/efficient therapeutic outcomes. Recent decades have seen a rise in the acceptance of cancer immunotherapy as a promising treatment alternative for cancer patients, with promising clinical results. Due to monoclonal antibodies' outstanding results as immune checkpoint inhibitors in preclinical and clinical studies and the Food & Drug Administration's (FDA) subsequent approval of these molecules for cancer therapy, the landscape of cancer treatment has changed. However, due to the short circulation duration of immune checkpoint inhibitors and shorter effect times, only a tiny proportion of patients and indications have benefited from the majority of cancer immunotherapies [1]. Both the field of oncology and the study of cancer biology are now actively researching immunotherapy. We will expand on current findings in preclinical studies and clinical trial outcomes from immune molecule-based therapies, such as cytokines, mAbs, ADCs, bi- or tri-specific antibodies, ICIs, and neoantigen cancer vaccines; and oncolytic virus-based therapies, immune checkpoints inhibitors, adoptive cell therapy and vaccine therapies in this review.

**II. Immunotherapy for triple-negative breast cancer: Development and Future Prospects.**

Based on the immunohistochemistry (IHC) expression of traditional hormone and growth factor receptors such as the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), as well as a proliferation marker Ki-67 protein expression, breast cancers have been divided into four major molecular subtypes. Worldwide, breast cancer continues to be the most common cancer in women. In the United States, it is anticipated that there will be 43,600 fatalities and around 281,550 new cases in 2021. A revised definition of breast cancer molecular subtypes was published by the 2013 St. Gallen International Breast Cancer Conference: IHC staining results for patient samples were used to calculate the percentages for luminal A (ER/PR+, HER2, Ki67+ 20%), luminal B (ER/PR+ 20%, HER2, Ki67+ 20%), HER2+ B2 (ER/PR+, HER2 over expression), HER2 over expression (ER, PR, HER2 over expression), basal-like triple-negative breast cancer (TNBC,ER−, PR−, and HER2−), and other subtypes[10]. Treatment options for breast cancer patients with the luminal A or luminal B subtypes include selective estrogen receptor modulators, aromatase inhibitors, and ER degraders. Patients who have HER2 over expression are candidates for treatment with tyrosine kinase inhibitors, antibody-drug conjugates, or monoclonal antibodies (mAbs) that target HER2. A major subdivision of the fourth breast cancer subtype known as TNBC with a negative expression of ER, PR, or HER2 is typically associated with poor prognosis due to a lack of targeted treatment options for this patient population, despite the fact that the three subtypes mentioned above can have favorable clinical outcomes because of their responsiveness to the targeted therapies. A subset of TNBC has been shown to have high tumor mutation burden (TMB) and high tumor-infiltrating lymphocytes (TILs), resembling the features seen on melanoma or lung cancers that can benefit from the treatment of ICIs, even though breast cancer patients in general do not respond well to immunotherapy. Consequently, the immunogenicity of this severe illness has created a window of opportunity for the creation of TNBC-targeting immunotherapies. A new era of immunotherapy for TNBC has begun with the FDA's recent approval of atezolizumab in combination with the chemotherapy drug nab-paclitaxel for the treatment of PD-L1-positive unresectable, locally progressed, or metastatic TNBC. The final market approval of the combination therapy was based on the positive findings from the Impassion130 clinical trial, where it was shown that patients receiving atezolizumab/nab-paclitaxel treatment for PD-L1-positive TNBC had median overall survival (OS) that was nearly 10 months longer than those receiving placebo/nab-paclitaxel treatment (NCT02425891).

**A. Immune Molecule Based Breast Cancer Therapy**

**Cytokine**

With the potential to strengthen the immune response against tumors, cytokines are important regulators of the innate and adaptive immune systems that control the proliferation, differentiation, survival, and effector functions of leukocytes through communication over short distances in paracrine and autocrine fashion. The use of exogenous cytokines for cancer treatment through modulating a patient's own immune system has been extensively pursued in fundamental and clinical research since the discovery of interleukin-1 (IL-1) as a "endogenous pyrogen" in 1953[9]. Currently, the FDA has approved two cytokines for use in cancer therapy [11]. The FDA initially approved interferon alpha 2 (IFN-) in 1986 as a single-agent cytokine treatment for cancer. Interleukin-2 (IL-2) was approved by the FDA as an immunotherapeutic cytokine monotherapy for the treatment of metastatic kidney cancer in 1991 and later for the treatment of metastatic melanoma in 1998 as a result of Rosenberg's seminal discovery showing that injections with T-cell growth factor, later named interleukin-2 (IL-2), can shrink tumors in humans. Members of the IL-2 family, IL-15 and IL-21 have both being studied to determine how effective they might be in treating cancer [9]. In 1993, GM-CSF was identified as a potent cytokine that promoted the development of myeloid cells. It is currently being studied in fundamental and clinical research as an adjuvant immunomodulator drug to induce anti-tumor immunity [12]. Many methods have been tested in the clinic to overcome the challenges associated with cytokine administration, including cytokines used in combination with checkpoint inhibitors, cytokines used in combination with anticancer mAbs to increase the antibody-dependent cellular cytotoxicity (ADCC) of these antibodies, and antibody-cytokine fusion proteins to promote tumor-specific immune responses. Clinical studies on the use of cytokines in combination therapy with oncolytic viruses are ongoing. Talimogene laherparepvec (T-VEC; ImlygicTM), an oncolytic herpes simplex virus that uses GM-CSF expression as an immune enhancer and was approved by the FDA for use in cancer immunotherapy in 2015 (T-VEC will be discussed more in the following section), demonstrates that cytokines can improve the oncolytic virus-induced immune response against tumors [9].

**Immune Checkpoint Inhibitor**

An ICI can activate the immune system, which is often inhibited by tumor cells or the tumor microenvironment, to target cancer cells. The FDA's approval of the anti-PD1 antibodies Keytruda (pembrolizumab), Opdivo (nivolumab), and ICI anti-CTLA-4 antibody Yervoy (ipilimumab) in 2014 and 2015 are the primary milestones of immunotherapy, heralding the start of a new era of cancer treatment [13]. Later, the FDA approved Libtayo (cemiplimab), Tecentriq (atezolizumab), Bavencio (avelumab), and Imfinzi (durvalumab), all of which are anti-PD1 and anti-PD-L1 antibodies [9]. Due to the small TMB (about 1 mutation/Mb) of breast cancers in comparison to melanoma or other tumors with high TMB, immunotherapy is not expected to be beneficial for individuals with breast cancer in general. But it has been shown that a subpopulation of TNBC exhibits high TMB (>10 mutations/Mb) and high TILs, characteristics seen in melanoma or lung tumors that potentially benefit from ICI treatment. Due to this aggressive disease's immunogenicity, there is now a chance for the development of immunotherapies that target TNBC [13-15].

**B. Neoantigen Cancer Vaccines**

Neoantigen cancer vaccines can stimulate the immune system to respond to a tumor-specific antigen (neoantigen), resulting in the development and proliferation of T cells that can recognize tumor antigens and inhibit tumor growth. Many vaccines have been developed to increase immunity against breast cancer because it is immunogenic, especially the TNBC subtype [16]. The efficacy of dendritic cell vaccines against HER2-positive breast cancer demonstrates that immunization against different onco-drivers can stop or delay the development of breast cancer. Additionally, neoantigens function as efficient targets for interception due to their high immunogenicity [17]. mRNA vaccines are promising next-generation vaccines that have ushered in a new era in vaccination science with the recent licensing of two COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2). The rapid development of mRNA vaccines for cancer immunotherapy is anticipated in the near future given the therapeutic effects of mRNA cancer vaccines that have been demonstrated in various clinical trials against multiple aggressive solid tumors.

**C. Oncolytic Virus-Based Therapy**

Oncolytic viruses (OVs) are a new class of therapeutic agents that promote anti-tumor responses through a dual mechanism of action that is dependent on selective tumor cell killing and the induction of systemic anti-tumor immunity. OVs are selectively replication competent in cancer cells, able to amplify themselves after initial administration, and potentially spread throughout the tumor. 2015 saw the FDA approve talimogene laherparepvec (Imlygic, OncoVEXGM-CSF, and T-VEC), a recombinant HSV-1, as the first oncolytic virus for the treatment of melanoma. Tumor cells can be selectively killed using oncolytic virotherapy. Additionally, an infection with an oncolytic virus results in the production of cell debris and antigens that boost the immune system [18]. The tumor is prevented from eluding the immune system and results in an immune response by a number of processes, including viral infection, oncolysis, the synthesis of new antigens, and the activation of cellular danger pathways. Other than T-VEC, a few OV candidates are now in the development stage. The recruitment of CD8+ T cells is crucial for boosting the effectiveness of immune checkpoint inhibitors, according to research by Niavarani and colleagues using vesicular stomatitis virus (VSV) in conjunction with an anti-PD-1 checkpoint inhibitor as a therapeutic regimen in experimental models of TNBC [19]. A naturally occurring, double-stranded RNA reovirus OV known as Pelareorep (Reolysin) was developed from the Dearing serotype 3 strain. One breast cancer patient in a phase I clinical trial employing pelareorep showed a stable illness after six or more weeks, while seven of the 19 patients showed some signs of local target tumor response activity. There are a few active clinical trials for the treatment of breast cancer using the adenovirus (Ad) serotypes 2 and 5, which are now being assessed as oncolytic adenoviruses. In addition to the combination therapies that combine OVs with ICI, OVs and CAR-T are also being developed to treat solid tumors like TNBC [20].

**III. Immunotherapy for Advanced Gastric Cancer**

The third most prevalent reason for cancer-related death is gastric cancer [21]. Patients with advanced stomach cancer have a dismal prognosis and a short lifespan of about one year due to the delayed diagnosis and lack of efficient therapy [22]. Radiotherapy, chemotherapy, and targeted therapy are the treatments that are most frequently utilized for advanced stomach cancer. Advanced gastric cancer is frequently treated with medications including imatinib, larotrectinib, entrectinib, and regorafenib [23,24]. However, the efficacy of these conventional treatments has been significantly constrained bymulti-drug resistance and tumor relapse. The most frequently used immunotherapies for advanced gastric cancer include chimeric antigenreceptor (CAR) T treatment, adoptive cell therapy, cancer vaccines, vascular endothelial growth factor A(VEGFA) antibodies, and immune checkpoint inhibitors (ICIs) . According to studies, ICIs such anti-PD-1/PD-L1 antibodies can successfully kill cancer cells by triggering the immune system. For cancerpatients, ICI clinical trials have shown efficacy and safety. It should be noted that a number of ICIs,including pembrolizumab, avelumab, sintilimab, tislelizumab, and ipilimumab, have been given thegreen light for use in combination with targeted therapy in the treatment of advanced gastric tumors [25] .

**A. Immune Checkpoint Inhibitors**

Ipilimumab was the first ICI to treat melanoma to receive approval in the globe in 2011 [28]. Since then, immune treatments have completely changed the approaches to treating advanced stomach cancer. Three categories of ICIs, anti-PD1/PD-L1 and anti-CTLA4 antibodies, predominate [29]. T cells and other immune cells that are activated can express PD-1. When PD-L1, the ligand for PD-1, binds to PD-1, immunological suppression and immune cell death follow. In advanced gastric cancer, PD-L1 is overexpressed, which causes tumor cells to resist immune response [30]. However, CTLA-4 protein has the ability to bind with B7-1/B7-2 with high affinity, inhibiting the CD28 signaling pathway, which is essential for T cell activation [31].

Nivolumab, a monoclonal antibody that inhibits PD-1, was approved by the FDA in 2014 for the treatment of advanced gastric tumors [32]. Through phase III clinical studies done across 40 Asian nations, the effects of nivolumab against advanced stomach cancer were investigated [27]. According to preliminary findings, nivolumab dramatically improved patient survival rates when compared to placebo. The human immune system depends on CTLA-4 in important ways. Although CTLA-4 and CD28 are homologous, B7-1/B7-2 can interact with CTLA-4 with a higher affinity [31]. CTLA-4 can therefore control or even prevent CD28 signaling. Tremelimumab and ipilimumab, two CTLA-4 inhibitors, have been studied in clinical studies for advanced gastric cancer [26]. For the treatment of advanced gastric cancer, a combination therapy using ipilimumab and nivolumab has been approved.

**B. Adoptive Cell Therapy**

Specific neoantigens with a high immunogenicity can be expressed by gastric cancer cells, activating the human immune system. Cancer cells can be identified and eliminated in this manner. However, cancer cells have the ability to produce immune-suppressing substances such lymphocyte-activation gene 3 (LAG-3), TGF-, prostaglandin E2, and IL-10 that prevent immune response, enabling them to avoid immune system identification and removal [33]. Adoptive cell therapy has been shown to be a successful method of treating advanced gastric cancer in individuals whose immune systems are unable to recognize and respond to cancer cells [34]. In order to effectively induce immunity to eliminate cancer cells, adoptive cell therapy makes use of a variety of immune cells, such as tumour infiltrating lymphocytes (TILs), lymphokine-activated killer cells, and cytokine-induced killer (CIK) cells [22, 35].

**C.**  **Anti-Angiogenic Therapy**

Vascular endothelial growth factor A (VEGFA), which is involved in the process of angiogenesis, which is the generation of new blood vessels, plays a crucial role in the development of gastric cancer . The modification of the immune response to cancer by VEGFA has the potential to allow tumor cells to evade the immune system’s guard . Advanced gastric cancer patients treated with bevacizumab and ICIs like atezolizumab, ramucirumab, and durvalumab have showed favorable efficacy in clinical studies [25].

**D. Cancer Vaccines**

The use of cancer vaccines, whichh can trigger immune responses against tumor cells in vivo, is another new treatment for advanced gastric cancer [36].The most extensively researched cancer vaccines are mRNA vaccines, which quickly transform the genetic information of an antigen into a protein to trigger an immune response and the killing of cancer cells [37]. Studies have shown that mRNA cancer vaccines outperformed conventional chemotherapy or targeted therapy in terms of both efficacy and negative effects [38]. Furthermore, preliminary clinical trials have demonstrated dramatically increased cytotoxicity against tumor cells when cancer vaccines and chemotherapies like cisplatin and 5-fluorouracil are combined [39].Results revealed that heightened humoral and cellular response to vaccined peptides was present in 50% of the patients treated with cancer vaccines.

**E. CAR-T Cell Therapy**

The CAR-T cell is particularly made to express synthetic receptors that can cause T cells to recognize a particular cancer antigen, which then triggers the host’s immune system to kill tumor cells [40]. Gastric cancer can be diagnosed and treated with the help of biomarkers like claudin 18.2 (CLDN 18.2), human epidermal growth factor receptor 2 (HER2), mucin 1, natural-killer receptor group 2 (NKG2D), epithelial cell adhesion molecule (EpCAM), mesothelin (MSLN), and carcinoembryonic antigen (CEA) [41].

**IV. Hepatobiliary Cancer**

Primary liver cancer and biliary tract cancers (BTC), which comprise hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and gallbladder cancer (GBC), are two types of cancer of the hepatobiliary system. Over 90% of liver cancer cases are hepatocellular carcinoma (HCC), which is the most prevalent kind [42]. One of the few tumors with rising mortality and incidence is HCC [43]. Cancers of the intra- or extra-hepatic biliary tree or gallbladder are referred to as biliary tract cancers (BTC). Because the majority of BTC are asymptomatic until advanced stages, they are uncommon and aggressive malignancies [44].Research and clinical trials are looking into the use of immunotherapy in HCC and BTC due to the lack of efficient systemic medicines and the unique immunological milieu of the liver[ 45].

**A. Immune Checkpoint Inhibitors**

With fewer undesirable consequences than cytotoxic chemotherapy, immune checkpoint inhibitors (ICIs) have been shown to be beneficial in the treatment of cancer. Inhibitory and stimulating immunoreceptors make up immunological checkpoints, which control the immune system. In order to generate an immunological milieu that is immunotolerant of the tumor cells, tumor cells can upregulate the expression of proteins that bind inhibitory immunoreceptors or downregulate the expression of surface proteins that block the activation of stimulatory immunoreceptors. ICIs are designed to prevent these interactions between immune and tumor cells in order to enhance immune cells’ anticancer activity [46].

The first CTLA-4 inhibitor for HCC was tremelimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor. The study showed that tremelimumab had a low rate of objective response and a tolerable safety profile. Theoretically, combined therapy may be more effective as a result [47].Nivolumab, a programmed death-1 (PD-1) inhibitor, was the first PD-1 inhibitor to be licensed by the FDA for the treatment of HCC in 2017 as a consequence of the Checkmate 040 and Checkmate 459 trials [48]. A PD-1 inhibitor known as pembrolizumab has shown effective in treating a number of malignancies. In the Keynote-224 trial, individuals with HCC who had progressed on sorafenib or were unable to tolerate it were treated with pembrolizumab. Pembrolizumab was effective and safe. As a result of this trial, pembrolizumab was approved by the FDA in 2018 for use In advanced HCC [49].

**B. Adoptive Cell Therapy**

Adoptive cell therapy involves harvesting tumor infiltrating immune cells from the patient and expanding them in the ex vivo setting. The harvested cells can also be genetically engineered for specific targets prior to expansion. After expansion, the cells are infused back into the patient.

**Tumor Infiltrating Lymphocytes (TIL) in HCC**

TILs are immune cells that have been collected, grown, and then reinfused into the patient with IL-2 to activate T cells. TILs are chosen for harvesting based on their capacity to detect tumor cells. The patient receives cydarabine/fludarabine for lymphodepletion prior to infusion. TIL is able to identify various tumor antigens and should, in theory, be more successful in locating and eliminating tumor cells.

**Tumor-Infiltrating Lymphocytes in BTC**

TIL is an area of BTC therapeutic research that is still being developed [50]. A unique and complicated microenvironment exists in BTC, including CCA, which promotes immunosuppression and the growth of tumor cells. Based on the presence or lack of immune cell infiltration within the tumor, CCA can be categorized into two groups. Immune cell infiltrated tumors are typically more sensitive to treatment [51].

**Chimeric Antigen Receptor T Cell (CAR-T Cell) in HCC**

Chimeric antigen receptor T-cell (CAR-T cell) treatment involves genetic engineering to target particular cancer-related antigens by harvesting T cells from the patient. These CAR-T cells recognize and bind the tumor antigens after they are reinfused into the patient, which causes their activation and cytotoxicity. CAR-T cells can deliver an ideal clinical benefit with fewer side effects by focusing on tumor-specific antigens that are barely expressed in healthy tissue. Numerous putative targets, including AFP, GPC-3, MAGE, NY-ESO-1, hTERT, NKG2DL, EpCAM, CD133, CD147, and MUC1, have been investigated in HCC [52].

**CAR-T Cell in BTC**

Effective targets for BTC are still difficult to find, but many HCC targets have been discovered. Mucin 1 (MUC1), which is abundantly expressed in malignant malignancies and linked to a poor prognosis and survival, is one possible target for CCA. Suimon et al. developed a fourth-generation CAR-T with anti- MUC1 domains and tested the effectiveness of the construct on CCA cells. The information revealed cytotoxic and disruptive effects on cancer cells, indicating potential for MUC1 as a CCA therapy target [53]. Integrin v6 is a promising target that is elevated in CCA but not in neighboring epithelial tissues. In malignancies, Integrin v6 is highly expressed, and this is linked to a lower survival duration. Targeting this antigen caused substantial levels of cytotoxicity in tumor cells, according to in vitro research [54].

**C. Vaccine Therapy**

**Vaccine Therapy in HCC**

The heterogeneity of HCC and the liver immune tumor microenvironment may be exploited by vaccine treatment. By providing antigens or dendritic cells with antigens, vaccines elicit a T cell response. Peptides known to be present in HCC, such as AFP, GPC-3, MAGE-1, NY-ESO-1, SSX-2, and hTERT, may be the focus of vaccine strategies. Neoantigens may also be used to create customized vaccines for specific patients. Neoantigens are particular protein sequences that are distinct to the patient and tumor and cause mutations in tumor cells [55]. A phase ½ vaccine trial using dendritic cells with AFP, GPC-3, and MAGE-1 antigens resulted in disease stabilization in 60% of patients versus the control group [56]. In a different phase ½ trial studied the safety and efficacy of the HepaVac-101 vaccine that targeted multiple antigens in 22 patients with early to intermediate stage HCC and suitable HLA haplotypes. The vaccine had an acceptable safety profile and had an immune response against HLA class I and II tumor peptides in 37% and 53% of patients, respectively [57].

**Vaccine Therapy in BTC**

Another area of research that is developing is BTC vaccines. Similar to HCC, the liver immune tumor microenvironment supports the development of vaccinations that specifically target BTC, albeit it has been difficult to create an effective vaccine. A DNA vaccination that targets CTLA-4 and PD-1 in CCA has shown promise in rat models [58]. The tumor antigens CD247, FCGR1A, and TRRAP were chosen as promising targets for the creation of an mRNA vaccine.

**IV. Nano-Driven Immunotherapy for the Treatment of Cancer**

The development of nanomedicine has provided an efficient replacement for the drawbacks of traditional immunotherapy. Numerous nanoparticle-based drug delivery systems have been created during the past three decades as means of administering anticancer medications, small interfering RNAs (si-RNAs), oligonucleotides, plasmids, cytokines, and antibodies to specific areas of the body [1]. Nanocarriers have received a lot of attention because they preferentially accumulate in tumors as a result of the increased permeability and retention (EPR) effect, which is a method for delivering anticancer drugs to specific tumors. Along with the EPR effect, nanoparticles can be modified with ligands to specifically bind to receptors overexpressed on the surface of cancer cells for active internalization and delivery of the therapeutic cargo. This reduces off-target effects while concurrently increasing treatment efficacy. By using nanoparticle-engaging delivery systems for immunotherapeutic chemicals that target the immune system and/or cancer cells, these advantages can be utilized for immunotherapy. Numerous studies have shown that adjusting the sizes, shapes, surface charges, and hydrophobicity of immunotherapeutic medicines successfully increased their distribution into tumor tissues or lymph nodes [4]. Additionally, nanoparticles have the benefit of enabling simultaneous administration of several immunotherapeutic medicines to the targeted areas, enabling multi-modal and more effective therapeutic activity. Using nanoparticles containing immunotherapeutic agents, controlled and stimuli-responsive medication release in response to intricate and immune-suppressive tumor microenvironments has also been impacted [1]. The main ways that nanotechnology-based immunotherapy inhibits tumor growth are through two distinct mechanisms: one involves triggering a powerful anti-tumor immune response during tumorigenesis, and the other involves enhancing tumor immune defense by modifying the immune suppression mechanism in the tumor microenvironment. Understanding the relationship between the immune system and smart nanomedicine has given the development of cancer treatments a strong boost thanks to the success of tumor immunotherapy.

**V. CONCLUSION**

Cancer immunotherapy has a significant advantage over conventional cancer treatments in that it not only cures primary tumors but also metastasis and recurrence. Scientists have been able to investigate new methods for immunotherapies by recognizing the behavior of cancer cells, identifying target antigens, and describing immune system pathways. The understanding that the traditional methods for evaluating treatment options in the age of chemotherapy and targeted therapies might not be appropriate for the new immunotherapies evolved over time. With the intervention of affordable and potential therapeutics new approaches can be developed to bridge the lacunae surrounding the grey areas in the field of immunotherapy. In order to augment responses rational combinations of immunotherapeutic agents and new immunotherapy technologies are being vigorously investigated. One of the most important future directions in cancer immunotherapy is identifying predictive markers which can predict the anti tumor effect and survival benefits before the implementation of immunotherapies the basis of their outstanding physiochemical features, such as their effective tissue-specific delivery function, vast specific surface area, and adjustable surface chemistry, nanomaterials are increasingly being used in cancer immunotherapy. As a result, nanotechnology has enormous promise for enhancing the effectiveness of cancer immunotherapy.

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