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Review Article

Novel Biotechnology and Immunotherapy Trends in Cancer Therapy

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Abstract

The quest for a potent treatment to combat cancer, which has emerged as the primary ailment afflicting mankind, has spurred the advancement of many approaches to investigate this affliction. Researchers and medical professionals have faced significant challenges in developing innovative treatments to overcome obstacles in cancer treatment and uncovering crucial insights into cancer development and progression. Comprehending the fundamental principles of the interaction between the human immune system and tumor cells has facilitated the development of novel and inventive approaches to cancer immunotherapy. The first progress witnessed in immunotherapy sparked enthusiasm among the scientific and clinical communities, since these approaches demonstrated significant potential for cancer treatment. However, there are other obstacles that currently hinder immunotherapy from being recognized as a truly effective treatment in the battle against malignant neoplasms. This review is trying to identify, assess, characterize, and define the main novel trends in immunotherapy and biotechnological therapies for cancer treatment.

Keywords: Biotechnology - Cancer Therapy – Immunotherapy - Monoclonal antibodies - Adoptive Cell Therapy – Cancer.

INTRODUCTION

Cancer is the leading cause of morbidity and mortality worldwide. In 2012, the World Health Organization (WHO) documented around 14 million incidences of cancer, and 8.2 million fatalities attributed to the disease (Figure 1 and 2). Moreover, it has been forecasted that there will be a 70% surge in new incidents during the next two decades. The projected cost for the treatment of newly diagnosed cancers in 2019 was estimated to be $510 billion, with a significant increase expected [1-3].

The medical sector allocates significant resources to the thorough examination of studies on cancer treatment [4]. Nevertheless, the intricate and distinctive attributes of cancer present numerous obstacles that impede the advancement of creating groundbreaking drugs for anti-cancer treatments. The primary obstacles involve the identification of novel specific targets within cancer cells and the efficient utilization of the immune system. Chemotherapy and radiation therapy, the dominant therapeutic methods, often produce unsatisfactory results and are greatly limited by their negative side effects [5, 6]. While some patients may initially exhibit a positive response to treatment, a significant portion of them experience future tumor recurrence and metastasis. Chemotherapy drugs can be categorized into two main groups. Synthetic drugs usually contain small molecules with distinct structures that specifically interact with one or a few biological systems involved in the progression of cancer [1, 7].

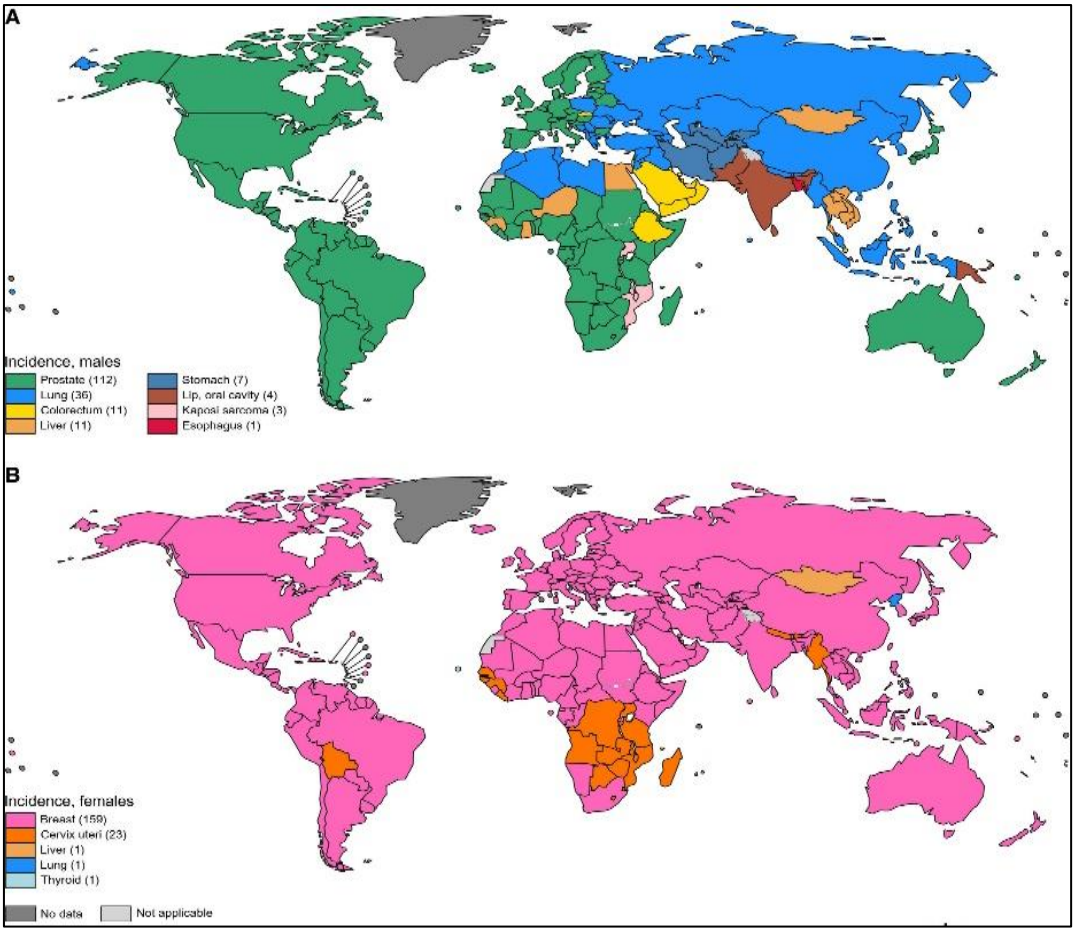

Figure 1: Global Cancer Statistics refers to the estimated incidence of cancer worldwide in the year 2020, as provided by GLOBOCAN [2]

An advantage of these drugs is their oral administration, exemplified by the tyrosine kinase inhibitors. Biotechnological drugs, categorized as the second group of chemotherapeutic treatments, are usually complex and substantial compounds derived from living organisms, frequently a human or humanized protein or peptide. A prime example of this latter classification is the monoclonal antibody [8, 9].

The advancements in biotechnology have enabled the development of innovative biotechnological drugs for the treatment of various diseases, including cancer, creating positive possibilities for future advancements [3]. The Organization for Economic Co-operation and Development (OCDE) asserts that patent data is a key asset for evaluating science and technology initiatives. Patent filings provide useful insights into the techniques and outcomes of creative projects, including their geographical spread and the relationships between networks and the related new technologies [4]. Unfortunately, malignant neoplasms possess the capacity to evade or counteract immune responses [2, 4, 8].

Malignant neoplasms have been discovered to impede the production of major histocompatibility complex (MHC)-I molecules, hence impeding the capacity of cytotoxic T-lymphocytes (CTLs) to identify tumor cells [9]. However, the immune system can remove cells that do not have or do not properly display MHC-I molecules on their surface by using natural killer cells (NK-cells). However, tumor cells can protect themselves from being destroyed by NK cells by displaying non-classical human leukocyte antigen (HLA)-G molecules on their outer membrane. In addition, tumor cells possess the capacity to induce the development of fresh blood vessels (angiogenesis) and can also recruit T-regulatory cells with immunosuppressive characteristics via chemical signals [10-12]. Consequently, malignant tumors may evade the body's immune system, leading to the formation of a distinct microenvironment around the tumor. Gavin Dunn and Robert Schreiber introduced the notion of "cancer immunoediting" as a sequential procedure consisting of three steps. During the early phase, the immune system's cells, such as NK cells, CD4+ T-lymphocytes, and CD8+ T-lymphocytes [1,13], eliminate cancerous cells. In the second phase, there is a state of equilibrium between the tumor cells and the immune system cells. In the third stage, the tumor inhibits the immune system, leading to a substantial decrease in its effectiveness [6]. Consequently, this stage concludes with the formation of a tumor that may be identified using clinical methods. Presently, the primary

goal is to create a highly effective immunotherapeutic strategy with minimal negative side effects. The objective of this treatment is to diminish the immunosuppressive impact of tumor cells and enhance the immune system's capacity to selectively eradicate the tumor [8, 9].

Immunotherapeutic approaches, like monoclonal antibodies, are designed to specifically target antigens present on the surface of cancer cells, with the goal of achieving precise and successful outcomes. Dendritic vaccines employ these antigens to enhance the immune system's ability to initiate and control immunological reactions [1, 11]. Tumor cells display unique antigens on their external membrane, which might provoke a specific immune response. Subsequently, tumor-associated antigens (TAAs) were discovered. These molecules are present in greater quantities or in a different state on the surface of cells compared to normal cells. Tumor biomarkers refer to tumor-specific antigens (TSAs), which are peptides expressed by major histocompatibility complex class I (MHC-I) on the surface of cells [12, 13].

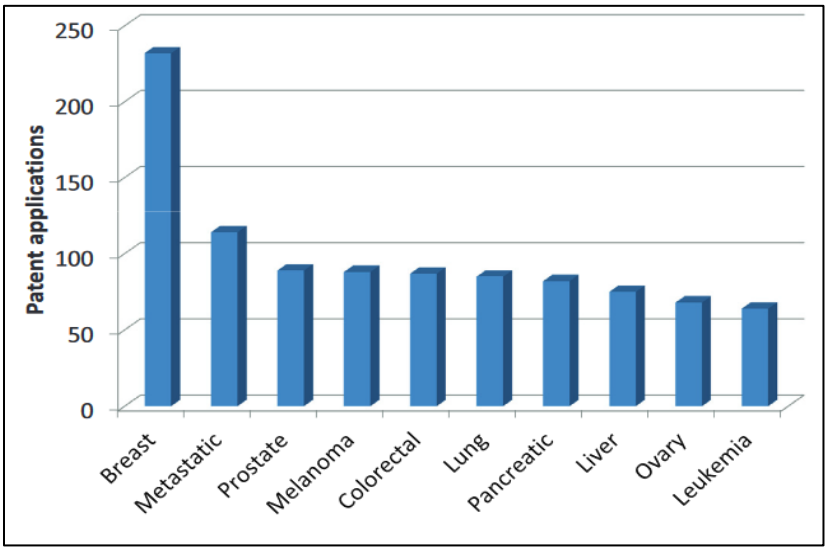

Figure 2: Patent applications categorized by specific types of cancer. Only the forms of cancer that had more than 60 applications been taken into account [5]

Monoclonal antibodies

Monoclonal antibodies (mAbs) that selectively target tumor cells were first developed in the 1970s. Therapeutic monoclonal antibodies of various types are commonly utilized in clinical practice. These include human antibodies (adalimumab), humanized antibodies (trastuzumab), which are composed of 90-95% human material, chimeric antibodies (rituximab), which are composed of 60-70% human material, and mouse antibodies (muromonab) [1, 3, 5, 11].

The primary objective of the study was to deliver monoclonal antibodies targeting tumor-associated antigens with the aim of eradicating tumor cells. Monoclonal antibodies (mAbs) can eliminate target cells through various mechanisms [7], including direct antibody action (which involves blocking receptors or delivering the toxic substance to the target), immune-mediated cell death, and targeted antibody impact on the vascular system and tumor microenvironment. The initial achievements in the clinical setting were linked to the later methodology [9, 11].

This medicine is used for the treatment of metastatic colorectal cancer, metastatic breast cancer (mBC), ovarian cancer (OC) [3], glioblastoma multiforme (GBM), and cervical cancer (CC). Bevacizumab, an angiogenesis inhibitor licensed by the FDA, is prescribed for several illnesses [3].

Studying antibodies that specifically target TAAs has great potential. Trostazumab, a pharmacological drug used to treat breast cancer, is an example of this phenomenon [12]. The technique by which it operates entails the inhibition of the excessive expression of human epidermal growth factor receptor 2 (HER2), a receptor that is accountable for conveying a signal to facilitate cellular proliferation. Pertuzumab, a recombinant monoclonal antibody, has undergone modifications to selectively target HER2 [15]. The distinction lies in the fact that trastuzumab and pertuzumab exhibit a significant affinity for regions of HER2, resulting in a synergistic impact [11].

Hematological malignancies, in contrast to solid tumors, originate from the bone marrow and lymphoid cells, which play a crucial role in the formation of blood. A diverse range of lymphoproliferative disorders, such as follicular lymphoma (FL), chronic lymphocytic leukemia (CLL) [14], mantle cell lymphoma (MCL), diffuse large B-cell lymphoma

(DLBCL), and other others, fall within the category of hematologic B-cell malignancies [15]. The decision to select B-cell transmembrane protein (CD20) as a therapeutic target was based on its vast distribution across several B-cell types, including those that display malignant characteristics. Rituximab, a chimeric anti-CD20 monoclonal antibody, is the standard treatment for hematologic malignancies such as non-Hodgkin's lymphoma, chronic lymphoblastic leukemia (CLL) [3], Wegener's granulomatosis, and microscopic polyangiitis. Empirical research has established the effectiveness of this medication in extending progression-free survival (PFS) and enhancing overall survival (OS) in individuals diagnosed with lymphoma [16]. Nevertheless, it has been demonstrated that those who underwent rituximab therapy exhibited resistance. The understanding of resistance mechanisms was accomplished through an examination of the trogocytosis process of monoclonal antibody-CD20 complexes, as well as the internalization of rituximab from the surface of malignant B-cells [17]. The monoclonal antibody (mAb) known as obinutuzumab has undergone glycoengineering and humanization to selectively bind to CD20 (type II). Furthermore, obinutuzumab demonstrates the ability to enhance direct cellular apoptosis and antibody-mediated cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis due to its modified elbow-hinge amino acid configuration [1, 4, 13].

The compound known as Brentuximab vedotin is composed of a human variation of immunoglobulin G1, which exhibits a specific affinity for CD30. The protease has the potential to degrade the linker that links the antibody to the drug monomethylauristatin E (MMAE) [16]. The pharmaceutical ingredient in question has demonstrated both safety and efficacy through several clinical trials. Presently, ongoing research is progressing towards the earliest stages of treatment. The FDA and European Medicines Agency (EMA) have granted licenses for the use of additional antibody-drug conjugates (ADCs) in the treatment of CD33-positive acute myeloid leukemia. ADCs, such as gemtuzumab ozogamicin, have the potential to be employed either in combination therapy or as an independent therapeutic intervention [7]. The permission for the use of trastuzumab emtansine in the treatment of HER2-positive breast cancer has been granted to patients who have previously received trastuzumab plus a taxane [17]. The authorization of isotuzumab ozogamicin encompasses the management of relapsed or refractory acute lymphoblastic leukemia (ALL) caused by CD22-positive B-cell precursor, both when employed in combination and as an independent treatment. In addition, there are now active endeavors to create and assess alternative antibody-drug conjugates (ADCs) via clinical trials. The medication candidates discussed above include Sacituzumab govitecan, Coltuximab ravtansine, Anetumab ravtansine, Glembatumumab vedotin, Trastuzumab deruxtecan, and GSK2857916 [18, 19].

While monoclonal antibodies (mAbs) have demonstrated considerable efficacy in conjunction with chemotherapy, they also exhibit a diverse array of adverse effects [20]. Typical adverse reactions encompass shivering, elevated body temperature, notable debility, cephalalgia, emesis, gastrointestinal disturbances, hypotension, cutaneous eruption, and specific complications may manifest in individuals with a predisposition to allergies. Infusion responses are the most often reported adverse effects. Adverse effects may arise from allergic responses to exogenous proteins or from the production of cytokines [9, 21]. All identified infusion reactions were observed in patients during the initial administration of rituximab. Nevertheless, these responses exhibited diverse degrees of intensity and encompassed a broad spectrum of symptoms. However, the utilization of monoclonal antibodies (mAbs) that selectively bind to an antigen may result in various adverse outcomes [22]. There exists a correlation between the administration of bevacizumab and several adverse effects, including gastrointestinal perforation, hypertension, hemorrhaging, nausea, diarrhea, thromboembolic problems, and, to a lesser extent, skin ulcers. Moreover, there have been documented instances of intestinal ischemia and hemorrhaging suggesting possible hazards [7, 23]. The potential toxicity of conjugated monoclonal antibodies (mAbs) may be increased when combined with dangerous chemotherapeutic medicines or radionuclides. The most frequently seen adverse effects in individuals who underwent treatment with brentuximab vedotin included peripheral sensory neuropathy (PSN), neutropenia, fatigue, nausea, anemia, upper respiratory tract infection (URTI), diarrhea, thrombocytopaenia, and coughing. There is a correlation between the presence of bispecific antibodies and increased levels of adverse effects. The central nervous system (CNS) may experience adverse effects as a result of blinatumomab treatment, including encephalopathy, aphasia, tremor, disorientation, and seizure [10, 24].

The adverse outcomes observed can be attributed to the binding of T-cells, which have been activated by blinatumomab, to the endothelium. The phenomenon of adhesion plays a crucial role in facilitating the movement of activated T-cells across the blood-brain barrier, hence allowing their infiltration into the central nervous system (CNS). T-cells within the central nervous system (CNS) induce an adverse inflammatory response [25-27].

Vaccines

In contemporary society, vaccines have emerged as the most effective technique for combating infectious diseases [29]. Considerable advancements have been made in the realm of disease prevention, specifically in the areas of yellow fever, smallpox,

rubella, polio, and measles [30]. There are two distinct classifications for vaccines: preventative and therapeutic. Both types of vaccines aim to induce targeted immune responses. Preventive vaccines are specifically formulated to counteract the existence of detrimental bacteria or cancer-inducing viruses, such as human papillomavirus (HPV), by the utilization of diminished or eradicated pathogens or virus-like particles (VLP). Autologous immune cells or peptides are commonly utilized as a fundamental approach in the treatment of malignant cells [7, 13, 30].

Several antiviral preventative vaccinations that are available for commercial use, including Cervarix®, Gardasil®, and Gardasil9®, have exhibited notable effectiveness. Gardasil® was authorized by the FDA in 2006 as the first immunization [31]. The vaccination consists of three recombinant vesicolipoproteins (VLPs) that are synthesized utilizing the major capsid protein L1 obtained from HIV strains 6, 11, 16, and 18. Furthermore, the amplification of the VLPs is achieved by including a neutral aluminum hydroxyphosphate salt [32, 33].

Gardasil9® was the subsequent version of the vaccine. A notable characteristic of this specific iteration, in contrast to its precursor, was its expanded array of antigens, which included HPV strains 31, 52, and 58. The formulation of Cervarix® consists of Vaccine Liquid Polymers (VLPs) derived from the major capsid protein L1 of papillomavirus (HPV) types 16 and 18. VLPs are produced in accordance with the AS04 standard. Cervarix® received approval from the FDA in 2007. The efficacy of immunization with these vaccines in terms of long-term durability remains unknown. The vaccinations Cervarix® and Gardasil® have shown a long-lasting ability to stimulate the immune system for at least 9 years, and in certain cases, up to 20-30 years [34-37].

Therapeutic vaccines are specifically formulated to activate certain CD8+ CTLs. It is assumed that the strategies utilized are derived from the interaction between MHC-I epitopes and TAAs. Various methods are employed to transport antigens, including the addition of adjuvants [12], to stimulate the activation of antigen presentation cells (APCs) in a living organism. They commonly employ a range of therapeutic vaccination approaches. One initial strategy is the creation of a peptide-based vaccine by the examination of amino acid sequences derived from tumor-associated antigens (TAAs), aiming to find potential minor histocompatibility complex I (MHC-I) epitopes [24]. The second method is stimulating dendritic cells (DCs) outside of the body using tumor-associated antigens (TAAs), which leads to the production of an anticancer T-cell response when they meet fully matured optimum antigen-presenting cells (APCs). The third approach entails employing nucleated tumor cells or their lysate, together with cytokines like GM-CSF and/or adjuvants [11, 27].

Furthermore, it is imperative to underscore the significance of experimental vaccines that utilize vesicles, sharing the common goal of addressing malignant illnesses [32]. Peptide-Based Therapeutic Vaccines entail altering immune system cells to recognize and counteract their own antigens by presenting major histocompatibility complex (MHC) peptide epitopes derived from tumor-associated antigens (TAAs). Immunizations that utilize one or more peptides are utilized either independently or in combination with adjuvants, such as Montanide, cytokines, or peptides, which are specifically administered to the antigen-presenting cells (APCs) [7, 14, 21].

Peptide-based vaccinations have demonstrated efficacy in the treatment of several cancer types, such as breast cancer, glioma, hematological tumors, renal cell carcinoma, and other malignancies. However, the ability of peptide-based immunization to eliminate large tumors is limited in terms of its immunogenicity [30, 32].

In addition, a vaccination utilizing short peptides can specifically activate CD8+ T-cells while disregarding CD4+T-helper cells, potentially limiting the effectiveness of the former [1,33]. To adequately investigate this subject matter, researchers have employed snail lymph hemocyanin (KLH) as an immunogenic xenoantigen to induce the activation of CD4+ T-cells. The efficacy of extended synthetic peptides containing epitopes MHC-I and MHC-II has been shown to be increased. However, although demonstrating more effectiveness, vaccinations that employ multipeptides or lengthy synthetic peptides still demonstrate a considerably restricted therapeutic effect [17, 23]. On the other hand, vaccines with neoantigens exhibit unique peptide sequences that are customized for each receiver, leading to a decreased probability of autoimmune responses. This characteristic confers significant benefits in terms of eliciting immune responses [34]. The NeoVax trial has yielded promising results, as reported by the Dana Farber Cancer Institute (DFCI). In addition, two patients received supplementary therapy consisting of the administration of anti-PD-1 inhibitors, leading to the successful achievement of complete tumor reduction [12, 35-37].

Tumor cell-based vaccinations typically comprise syngeneic, allogeneic, or autologous primary tumor cells that have been recently obtained and subjected to irradiation. Cytokines, such as GM-CSF, can be used to modify these cells. One instance illustrating this phenomenon is the GVAX vaccine, which employs genetically engineered tumor cells that have undergone mitotic inactivation and possess the GM-CSF cytokine genome [12, 38]. The alteration results in an immunostimulatory impact. In addition, it is worth noting that immunizations possess the capacity to

incorporate viral pathogens, such as the Newcastle disease virus. The vaccinations are administered via subcutaneous injection using an oil emulsion, such as incomplete Freud's adjuvant (IFA), or a saline solution. The procedures described above were subjected to clinical testing in a designated study and then implemented as constituents of a combinational vaccination [12, 38]. In this trial, CRS-207, a genetically engineered strain of Listeria bacteria capable of producing TAAs (mesothelin), was administered to persons diagnosed with pancreatic cancer. The administration of CRS-207 was conducted with or without the utilization of GVAX. The GVAX vaccination employed pancreatic cell lines derived from allogeneic malignancies [39].

Attempts have been made to incorporate this methodology with supplementary therapy modalities, particularly immune checkpoint inhibitors (ICIs). Inconclusive results were obtained from phase II clinical trials investigating the efficacy of Cy/GVAX + pembrolizumab in the management of advanced mismatch repair proficient (MMRp) colorectal cancer [11, 17, 40].

Gene therapy Adoptive Cell Therapy

Gene therapy has exhibited considerable potential as a therapeutic modality for several ailments, encompassing specific types of cancer [17]. The technology being proposed involves the incorporation of one or more corrected genes created in a laboratory setting into the cellular composition of an individual [41]. Gene therapy involves a range of techniques, including gene replacement, protein alteration, gene activation, and gene inhibitory. The management of cancer encompasses three principal approaches. After suppressing oncogenes, the primary approach is activating or introducing tumor suppressor genes. The third method involves the integration of genetic material that contains instructions for producing toxic substances [13, 42].

There are two unique approaches available for the introduction of modified genes into a specific cell: adoptive cell transfer and the introduction of a gene vector into the patient's body to aid the target cell delivery of the genes. A wide variety of species, including viruses, bacteria, and liposomes, are commonly found as gene carriers [27, 40]. The biggest candidates for gene therapy patents are OPKO, a multinational pharmaceutical and diagnostics corporation that was acquired by Roche in 2014 [43].

The main focus of OPKO applications is the use of short interfering RNA (siRNA) molecules, which can attach to the nucleotides of messenger RNA (mRNA). This messenger RNA (mRNA) is essential in the translation of proteins associated with cancer and can be used to cause silence. This paper presents a case study that demonstrates the selectivity of a nucleotide sequence of small interfering RNA (siRNA) towards the messenger RNA (mRNA) responsible for encoding vascular endothelial growth factor (VEGF). This protein is essential for facilitating angiogenesis, the process of generating new blood vessels, and is especially prevalent in cancerous cells [44-48].

Health and Human Services (HHS) places significant emphasis on the utilization of genetically engineered immunological T cells that exhibit a pronounced affinity towards tumor-associated antigens (TAAs) [49]. T cells are often treated using purification and isolation methods, which lead to the acquisition of a modified receptor that can specifically target tumor cells. Furthermore, the receptor of these genetically engineered T cells is subjected to the incorporation of an external DNA gene responsible for encoding microRNA. Moreover, these applications employ two separate classifications of receptors [1, 50]. The initial categorization concerns the T cell receptor (TCR), which is bolstered by diverse alterations referred to as chimeric antigen receptors (CARs) [51]. The general populace now has access to conjugated antigen receptors (CARs), which are synthetic receptors. While multiple clinical trials have shown positive therapeutic results, the main obstacle for this possible method is to enhance the survival and growth of T-cells [28, 52]. Santaris Pharma primarily emphasizes the application of Locked Nucleic Acid (LNA), which are oligonucleotides composed of one or more nucleotide components. During the LNA process, the ribose ring undergoes entrapment by means of a methylene bridge formation, which serves to connect the 2'-O atom with the 4'-C atom. Long non-nucleotide analogs (LNAs) display enhanced stability and a heightened propensity to establish pairings with a complementary nucleotide strand as compared to RNA molecules [13, 49].

The LNA exhibits a distinct affinity for the mRNA of PDZ-binding kinase (PBK) in a biological setting, leading to the inhibition of mRNA production and a subsequent reduction in PBK expression [18]. Protein kinase (PKK) is a hormone that governs the progression of the cell cycle and is only triggered during the mitotic phase. Nevertheless, it is overproduced in malignant cells. The LNA exhibits a clear inclination towards the messenger RNA (mRNA) of aurora kinase B. Aurora kinase B, a protein cluster, is essential during the mitotic phase and is highly expressed in cancerous cells [31, 50].

Oncolytic Viruses

A vast array of viral strains, such as adenovirus, herpes simplex virus, poliovirus measles, smallpox virus, maraba virus [27], Coxsackie virus, and Newcastle disease virus, have been effectively utilized in the development of recombinant viral vectors [12].

These viruses have been employed in various approaches for the treatment of cancer [51]. The primary

constituents of most viruses consist of three fundamental components, namely the genome, the capsid, and the lipid envelope. Every viral variant possesses a distinct structure, as demonstrated by its extensive array of modifications when employed to combat a tumor [52]. To provide an example, DNA viruses possess the ability to contain significant eukaryotic transgenes that enhance therapeutic effectiveness or modulate the immune system, along with DNA polymerases that speed up replication [33, 53]. Similar to reoviruses, RNA viruses possess a reduced genome size, enabling them to traverse the blood-brain barrier and specifically target tumors within the central nervous system. Since the early 1950s, notable advancements have been achieved in the realm of oncolytic viruses (OVs) as a form of immunotherapy. However, during the past 15 years, there has been a notable surge in the exploration of the oncolytic properties of this specific therapeutic approach. In the therapy of malignant disorders, oral contraceptives (OVs) are employed as a diverse tool [17, 22, 54]. Viruses and the immune system can interact with tumor cells in a diverse range of ways, resulting in different anticancer effects. The multiplication of oncogenic viruses (OVs) in cancer cells ultimately leads to their demise, causing the spread of tumor-associated antigens (TAAs) and other chemicals [55]. This procedure provokes the activation of both the innate and adaptive immune systems. Certain wild-type ovarian cancer cells possess the capacity to identify extensively expressed receptors on the surface of tumor cells or other anomalous substances or pathways within tumor cells, enabling them to specifically target them [37]. Coxsackievirus A21 (CVA21) exhibits an inherent affinity for tumor cells by recognizing many receptors and intercellular adhesion-1 molecules (ICAM-1/CD54) on the outer membrane of tumor cells. The identification indicated above amplifies the virus's ability to infiltrate, replicate, and ultimately eradicate cancerous cells [38-40]. The safety and efficacy of an oral vaccination (CAVATAK®) containing CVA21 in eliciting an immune response against melanoma have been substantiated by prior research. The virus referred to as Parvovirus H1 (H1-PV) demonstrates a clear preference for replicative and transcriptive components within neoplastic cells, in addition to a malfunctioning type I interferon-mediated antiviral mechanism. Phase I/IIa clinical trials have demonstrated the safety and immunogenic effectiveness of ParvOryx (wild type H1-PV) in treating GBM. Reolysin® (pelareorep) [41], a proprietary variant of reovirus, has been granted authorization by the Food and Drug Administration (FDA) as an orphan medication for the management of gastric and pancreatic cancer [51, 52].

Nevertheless, this approach presents a challenge with regards to the immune response against the pathogen. The immune system exhibits a notable preference for viral antigens, hence diminishing the efficacy of therapeutic therapies [53-55]. Numerous other approaches and procedures have been employed in an effort to address this issue. Dendritic cells (DCs), mesenchymal stem cells (MSCs), T-cells, and cytokine-induced killer cells (CIKs) are among the host cells that harbor the virus [54]. The primary role of host cells is twofold: firstly, they serve to safeguard the virus from immune neutralization, and secondly, they hinder the virus's uptake by the reticuloendothelial system, thereby facilitating its migration towards a prospective site for tumor formation [14]. Moreover, the capacity of viruses to undergo reproduction within neoplastic cells is a critical element of the therapeutic strategy [55]. Certain viruses possess an inherent affinity for tumors, whereas others necessitate genetic modifications to specifically target and infiltrate tumor cells. A range of techniques are employed to enhance the precise targeting of viruses and maximize the effectiveness of replication. The primary aim of genetic changes in ovarian cancer (OVs) is to eliminate virulence genes to assure safety, while concurrently incorporating foreign genes to enhance the efficacy of anticancer therapy and tumor selectivity [17, 56].

Currently, numerous preclinical and clinical studies are being conducted to evaluate the efficacy of this therapy when combined with conventional cancer therapies including radiotherapy and chemotherapy. In addition, ongoing research efforts are actively exploring novel approaches to immunotherapy, such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapy [1, 21, 54].

The dual use of Reolysin®, carboplatin, and paclitaxel has demonstrated increased effectiveness in addressing the progression of malignant melanoma [22]. The trial attained a response rate (ORR) of 21%, an overall survival (OS) of 10.9 months, and a median progression-free survival (PFS) of 5.2 months [14]. The simultaneous administration of ONYX-015, an adenovirus with E1B deletion that replicates in p53-deficient human tumor cells, along with cisplatin and 5-fluorouracil, has shown a significant improvement in the overall response (OR) by up to 65% compared to monotherapy, where the OR was only 15%. A phase I/II clinical trial was conducted to examine the effectiveness of T-vec in treating squamous cell carcinoma of the neck and head. Intravenous injections of T-vec were delivered to patients in combination with cisplatin chemotherapy and radiation. A neck dissection was performed within a time frame of 6-10 weeks following the treatment [55]. The combination of OVs with ICIs demonstrates a synergistic effect. In the tumor microenvironment (TME), oligodendritic cells (OVs) have the ability to recruit CD8+ T-cells and natural killer (NK) cells [56], leading to the increase of PD-L1 expression on the outer membrane of tumor cells. By eliminating the absence of immune cells in the tumor microenvironment (TME), this process enhances the effectiveness of anticancer therapy by inhibiting immune checkpoint inhibitors (ICIs). Phase Ib clinical research has provided evidence of the effectiveness of this combination in the treatment

of patients diagnosed with progressing melanoma. Patients that exhibited a positive response to therapy demonstrated a notable augmentation in CD8+ T-cell count, alongside an upregulation of the PD-L1 protein and the IFN-γ gene expression on certain cancerous cells. The utilization of OVs in conjunction with CAR T-cell treatment possesses the capacity to surmount numerous intratumoral obstacles [17, 33, 41, 56].

The administration of OV elicits the eradication of neoplastic cells, hence facilitating the infiltration of CAR T-cells into the tumor site and concurrently triggering the secretion of TAAs [58]. These antigens elicit a T-cell response, resulting in a symbiotic relationship between CAR T-cells and cytotoxic T-lymphocytes in the eradication of several tumor cell types. The present research is centered on investigating the efficacy of OVs in conjunction with CAR T-cell treatment in mice models, which has demonstrated a significant and noteworthy antitumor impact [22, 59, 60].

Conclusion and Future Perspectives

Cancer is the predominant medical condition observed in patent applications. Patent applications often focus on topics such as RNA interference, CART- cell therapy, gene therapy, monoclonal antibodies, adoptive cell therapy, and novel vaccine peptides. The number of recently established cancer treatments that are specifically customized has been steadily increasing, partly due to the growing use of biological agents. An analysis of the fundamental mechanisms by which biotechnology pharmaceutical's function, as outlined in patent applications, uncovered alterations in the primary aim of safeguarding. The largest proportion consists of antibodies, followed closely by gene therapy and therapeutic proteins.

A crucial obstacle in attaining optimal outcomes in cancer therapy is assuring the specific effectiveness of the medicine on malignant cells, while safeguarding the vitality of normal cells and limiting any adverse repercussions. The majority of patents submitted within the past five years have focused on products that exhibit a strong attraction to cancer cells. These include new arrangements of monoclonal antibodies (mAbs) that have both bi and multispecific binding sites, as well as smaller antibody fragments that have improved tissue penetration and accumulation in tumor cells.

Gene therapy exhibits potential as a viable substitute for cancer treatment in the foreseeable future, particularly within the framework of adoptive cell transfer. This method decreases the probability of negative responses, as only the cells that are genetically modified in a controlled laboratory environment get the genetic material. When choosing a strategy, it is crucial to prioritize the most efficient methods by thoroughly assessing the advantages and disadvantages of each alternative. The utilization of cytokine therapy has significantly enhanced the efficiency of immune cells, facilitating the eradication of malignant tumors. However, this advantage also comes with a drawback in this method as it triggers an increase in autoimmune activity, resulting in the incidence of notable side effects.

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