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Developmental Pathways of Cancer Immunotherapy: Successes and Challenges

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Abstract:

The history of cancer vaccine research goes back to 1891 when the famous Coley's toxin was administered to boost a patient's immune system by Dr. William Coley in New York. Since then, there has been intensive research in developing cancer vaccines, with a lot of promise but with limited clinical success, until recently. This is evident from the fact that the FDA approved the first cancer vaccine only in 1991. This all changed with the discovery of checkpoint inhibitors in 1995. The past two decades have seen tremendous advancements in cancer immunotherapy, a form of cancer vaccine which uses the body's immune system to fight cancer, rather than just train to recognize cancer. Improved understanding of mechanisms by which the cancer cells evade the immune system have led to therapeutic treatments to counteract the evasion mechanism. In this review, I have examined the evasion techniques employed by cancer cells to hide from the immune system, advancements in the counteracting approaches to reverse these roadblocks which have led to several different cancer immunotherapies and have identified several gaps in our understanding of cancer, all of which are potential areas for further research. These are promising times in the fields of immunology and cancer immunotherapy research.

Keywords — **Immunotherapy, checkpoint inhibitors, CAR T cell, oncolytic virus, cancer vaccine**

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I. INTRODUCTION

Immunotherapy, the fifth pillar of cancer treatment after surgery, radiotherapy, chemotherapy, and molecularly targeted therapy, has been a highly promising treatment option since the late 1990s [1]. Cancer immunotherapy refers to any treatment that uses the body's immune system to defeat cancer; it includes therapeutic vaccines and several other novel treatment methods [2]. Treatment vaccines aim to help the immune system recognize tumor antigens: the proteins found in cancer cells. When antigens are identified, the immune system attacks and destroys the cancer cells by using the various components of the innate and adaptive immune systems [2].

However, this is not always enough as cancer cells have developed many tricks to evade the immune system [2]. Therefore, despite decades of intensive research and promise shown in pre-clinical findings with cancer vaccines, results had not translated into many curative therapies until the last decade [2]. Cancer cells can inhibit the immune cells from destroying them using several mechanisms. This has led to novel treatment approaches to counteract the various evasion strategies employed by the cancer cells [2].

Basic research in immunology, study of the immune system, has been instrumental in the rapid advancements in immunotherapy. Since 2011, many treatments have been approved by the US FDA and many more are under active research and trials [1]. Each treatment option modifies a different component of the immune system [1]. Immune checkpoint inhibitors unleash the power of the T-cells by releasing certain brakes which would otherwise prevent the immune cells from destroying the cancer cells, despite detection [1]. Adoptive cell therapies use engineered immune cells to amplify the

cancer killing power, by providing more cancer-targeted immune cells [2]. Cytokine therapy enhances the immune cell function using proteins called cytokines [1]. Monoclonal antibodies bring immune cells into close contact with cancer cells and activate them [1]. Oncolytic viruses preferentially infect cancer cells and release inflammatory agents that trigger cancer fighting T-cells [1]. These novel methods distinctly differ from cancer vaccines that work against something that causes cancer, unlike immunotherapy that works against cancer cells [3].

A broad overview of the immunotherapy methods currently in use and being researched is presented here. Improvements in the clinical efficacy of these treatments are a continuing challenge. One aim of this review is to inspire future generation (pre-university students) of aspiring cancer researchers by providing concise exposure to the subject matter without overwhelming them with too many post-doctoral level details.

The complexities and challenges in developing immunotherapy treatments are enormous, but so are the potential benefits. The costs of such treatments can be prohibitively expensive, so innovative cost-cutting solutions must be a parallel focus for such treatments to become mainstream. It all begins with a thorough understanding of the science behind cancer immunotherapy, encompassing the fields of immunology and cancer biology.

II. OVERVIEW OF IMMUNE SYSTEM

Knowledge of the human immune system is fundamental to a proper understanding of immunotherapy and cancer vaccines.

There are two types of immunity: innate and adaptive [4,5]. Innate immunity is present at birth and provides a generalized (not specific) and immediate response to foreign invaders: it does not have to be learned by exposure to invaders. Innate immunity, unlike acquired immunity, has no memory of the encounters, does not remember specific foreign antigens, and does not provide any ongoing protection against future infection [4]. The cells that make up the innate immune system, called effector cells, include natural killer (NK) cells, neutrophils, macrophages, etc [6].

Adaptive immunity, on the other hand, develops after birth and is antigen specific [5]. Adaptive immunity is mediated by B (bone marrow derived) and T (thymus derived) lymphocytes (specialized white blood cells) [6]. B cells work by producing antibodies (humoral immunity) against foreign antigens aiming to block their impact on cells and tissues, while T cells recognize and eliminate diseased cells (cellular immunity). An effective immune response against an antigen involves a combined effort by both the innate and the adaptive immune system. Cells of the innate immune system produce cytokines and chemokines, which are essential for activation of other immune cells, including B and T cells of the adaptive immune system [6].

Immunological memory, a hallmark of the adaptive immune system, is a critical concept for understanding vaccine efficacy and the body's ability to combat recurrent infections [6]. This memory is formed during the initial encounter with a pathogen or its antigens, whether through natural infection (pathogen) or vaccination (cognate antigen). In the initial encounter, the adaptive immune response is initiated, meaning T cells (helper and killer) and B cells (produce antibodies) are activated. Some of the T cells and B cells are memory cells which retain information about the antigen. When the body encounters the same pathogen again, the rapid recognition and response often neutralizes the pathogen before it can cause significant illness or disease. The secondary immune response is typically more robust than the primary response, with higher levels of specific antibodies and a more efficient activation of T cells [7]. This ensures effective clearance of the pathogen, often preventing the development of symptoms and providing long-term protection [7].

III. ADVANCES & CHALLENGES

Cancer cells are not like foreign pathogens that the innate immune system can easily recognize and destroy. They are not conventional antigens, as

viruses and bacteria are. Instead, they are mutated versions of the body's own cells [8]. That means the immune system does not get the signal to fight cancer cells the way it does when germs are encountered.

Cancer cells have also developed many tricks to hide from the immune system. During disease progression, cancer cells evolve and find ways to evade the immune system by: (1) reducing the amounts of protein markers that the immune system targets to recognize cancer cells, (2) triggering certain brakes on T-cells that prevent them from killing the cancer cells, and (3) releasing molecules that weaken the immune system so that the cancer can continue to grow and spread [1,2]. Counteracting these tricks is the key to developing new treatments. Some of the challenges posed by tumor cells and novel ways to thwart them are discussed below.

Tumor Antigen Heterogeneity

Tumors are not homogeneous; antigens on tumor cell surface are not identical at all locations. The same cancer type in two patients also show different antigens on the tumor cell surface (inter-patient heterogeneity) [8]. Metastasized tumor masses, in the same patient but at different locations also show heterogeneity (intra-patient heterogeneity) [8]. Furthermore, therapeutic treatments change the subpopulations differently, and some become more resistant.

Tumor heterogeneity has been a barrier in the case of immunotherapy [1,8]. To overcome this problem, multiple therapies are needed, such as combining chemotherapy with immunotherapy [1]. A deeper understanding of the various factors that impact tumor heterogeneity is needed. Advances in high-level analytical techniques and artificial intelligence (AI) to analyze large datasets will speed up the process of understanding and devising appropriate solutions.

Neoantigens

In cancers of the blood, the antigen presented on tumor cell surface is relatively uniform and stable [9]. Not so in the case of solid tumors where heterogeneity is a barrier to immunotherapy [8]. TAA or tumor associated antigens are self-antigens (part of the host) and have elevated levels on tumor cells and lower levels on healthy cells [10]. Being self-antigens, the immune system does not recognize and attack unless the levels are high.

However, tumor-specific antigens (TSA) are found on cancer cells only, not on healthy cells [10]. These are neoantigens (new antigens), formed due to mutations in the tumor itself [10]. Cancer initiation and progression are due to repeated mutations that occur and the chances of neoantigen expression increase with each mutation [11]. Neoantigens are foreign antigens, hence they elicit a stronger response from the immune system and are promising targets for cancer treatment.

TAA are easier to identify and can be common to many patients, unlike TSA, which is specific to individual patient tumor. Screening and identifying TSA is costly and laborious, but some studies have shown promising results unlike the mediocre results using TAA for target. [11].

Downregulate antigen presentation molecule (MHC I)

Cancer cells can downregulate or lessen the expression of MHC-1 molecules. Since cytotoxic T cells must recognize the antigen-MHC I complex to get activated and destroy it, any alteration of the MHC I molecule can evade detection [12]. One way to downgrade MHC I expression is by reducing the MHC I molecules on tumor surface. T cells detect cancer cells by recognizing MHC I molecules. So, detection and killing of cancer cells by T cells is impaired if number of MHC I molecules is reduced. There are various other mechanisms to downregulate MHC I expression [12].

There is a clear correlation between reduction in MHC-I expression and worse response to Immune checkpoint inhibitors (ICI) therapy [12]. Some MHC-I downregulations are reversible. In such cases, therapeutic options may upregulate and can be used in conjunction with ICI treatment. Several such strategies have shown promise and are under active investigation [12].

IV. IMMUNOTHERAPY TREATMENTS

Immune Checkpoint Inhibitor (ICI)
(release brakes of the immune system)

Two signals are needed to activate the T cells [13]. This is to make sure that unnecessary activation does not occur as it can damage self-cells and engender an autoimmune disease.

Signal 1: T cell receptor (TCR) binds to MHC/TAA complex on the surface of cancer cell. Any tumor protein or glycoprotein, synthesized by the cancer cell with MHC attached, is TAA.

Signal 2: co-stimulatory signal. This signal is also required to activate T cell. Examples are CD80/CD86 on tumor cell and CD28 on T cell (Fig. 1) [13]. With both signals present, T cell is activated and can enter clonal expansion resulting in several T cells, some of which are killer T cells (destroy cancer cells) and others are memory T cells. This co-stimulatory signal is an upregulating (plus) signal as it begins T cell activation. Accordingly, the molecules are called stimulatory checkpoint molecules [14].

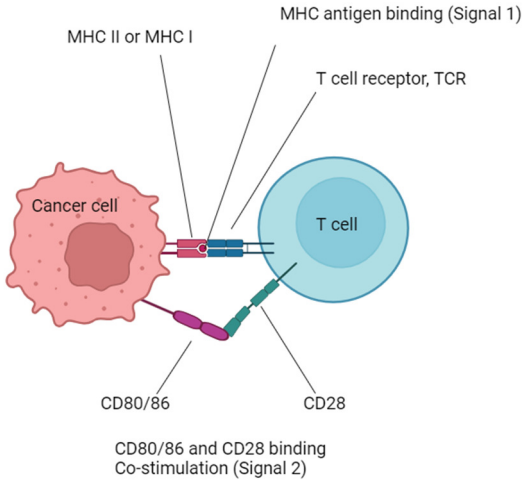

Fig. 1. Costimulatory signal [13]
(drawing prepared using BioRender)

Just as there are co-stimulatory signals for activation, there are also co-stimulatory signals for inhibiting activation [13]. An example is PDL1 in tumor cell and PD1 in T cell (Fig. 2). When these receptors bind, the T cell is not activated even though the T cell has latched on to the cancer cell. Without activation, cancer cell cannot be destroyed since there are no killer T cells produced. This signal is negative signal as it inhibits T cell activation. It is also called down regulating signal [13].

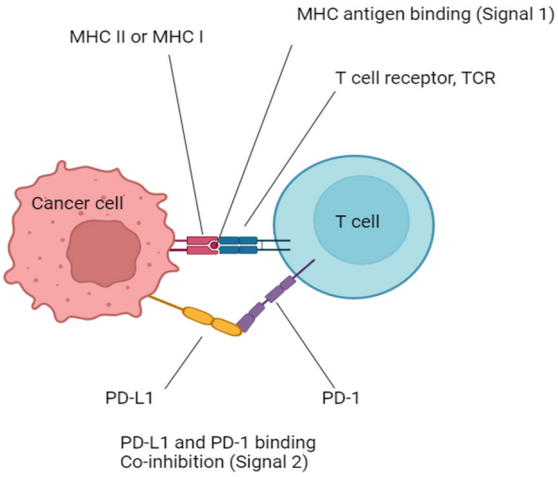

Fig. 2. Coinhibitory signal [13]
(drawing prepared using BioRender)

Such inhibitory signals are mediated by surface proteins called checkpoint molecules. Such inhibitory checkpoint molecules play an important role in controlling immune responses by modulating the length and magnitude of immune responses to avoid damage to healthy tissues [14]. In a healthy host, an intricate balance is maintained between the activation and inhibition of immune responses. Tumors, however, shift the equilibrium towards the inhibitory signals by activating the checkpoint molecules [15]. The T cell's activation is switched off, thereby preventing the T cells from destroying the cancer cells.

Adding an antibody to PD1 or PDL1 (Fig. 3) could block the inhibitory signal by latching to the respective T cell or cancer cell receptor, thus blocking it from latching to the other cell [13]. With immune checkpoint disabled, the T cell can destroy the cancer cell.

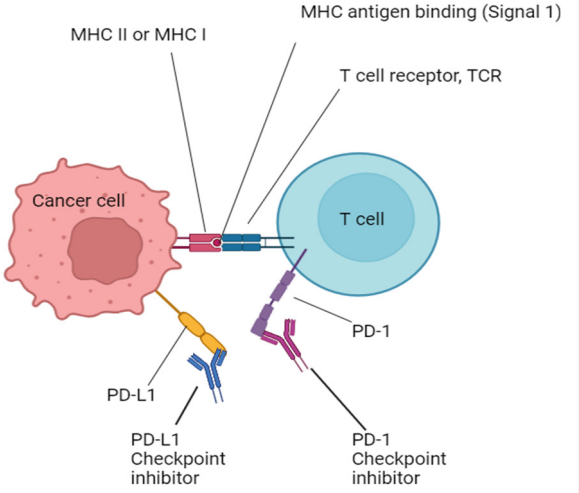

Fig. 3. Checkpoint inhibitor antibody [13]
(drawing prepared using BioRender)

Checkpoint inhibitors are a class of immunotherapy drugs that introduce such antibodies to foil the inhibitory signal.

CTLA4 is a checkpoint inhibitor expressed on T cells. Ipilimumab, a monoclonal antibody, was developed for human use [6, 16] and approved by the FDA in 2011 for the treatment of metastatic melanoma or cancers that cannot be surgically removed.

PD1 is another checkpoint inhibitor. The monoclonal antibody, Nivolumab, was approved by the US FDA for treatment of advanced melanoma, metastatic renal cell carcinoma, Hodgkin's lymphoma, urothelial carcinoma, etc. Pembrolizumab, another PD-1 monoclonal antibody was approved for advanced cases of the above diseases, head and neck cancer, and lung cancer [6].

Twelve checkpoint inhibitor immunotherapies have been approved by the US FDA as of Dec 2023: CTLA-4 inhibitor (ipilimumab, tremelimumab), PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab, dostarlimab, retifanlimab and toripalimab), PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) and LAG-3 inhibitor (relatilimab) [17, 18].

Adoptive Cell Therapy (CAR T cells)
(boost the cancer killing power)

We have seen how cancer cells avoid detection by downregulating MHC I and by displaying the checkpoint molecules on their surface so that the T cells spare them from destruction thinking that they are normal cells. The T cells must be re-educated to make them better at recognizing cancer cells despite the trickery employed by the cancer cells. The Chimeric Antigen Receptor (CAR T) cell therapy counteracts both deceptions [19].

The patient's blood is filtered through a machine to collect T cells and other while blood cells [19]. Then an engineered foreign particle is introduced and mixed with the T cells [19]. These particles have receptors that attach to the TCR. The particle is then taken in by the T cell and genetic instructions are given telling the cells to produce CAR receptors, making them into CAR T cells [19]. When enough CAR T cells are produced in the laboratory, they are infused into the patient [19].

The CAR T cells then detect cancer cells in the body, get activated and destroy cancer cells. The CAR T cells can directly find specific markers in cancer cells without the need for MHC I (CAR T cells are MHC independent). The CAR T cells are also not affected by checkpoint inhibitors. The CAR T cell treatment is customized for every individual [19].

Since 2017, six CAR T-cell therapies have been approved by the Food and Drug Administration (FDA). All are approved for the treatment of blood cancers, including lymphomas, some forms of leukemia, and, most recently, multiple myeloma [1].

ICI and CAR-T immunotherapy, however, do not work in all cases. They work better for hematologic cancers but not so well in solid tumors. This suggests that cancer cells have other tricks up their sleeve for

evading the immune system. One recent discovery pointed to growth of nanotube structure between tumor cell and T cell which was a conduit for draining mitochondria from the T cell to feed the tumor cell (Fig. 4), resulting in T cell population declining rapidly [20]. By using an inhibitor of nanotube formation with checkpoint inhibitor on mice, tumor growth was reduced more than when using ICI drugs alone [20]. Compounds that specifically target nanotube formation will provide another pathway for immunotherapy.

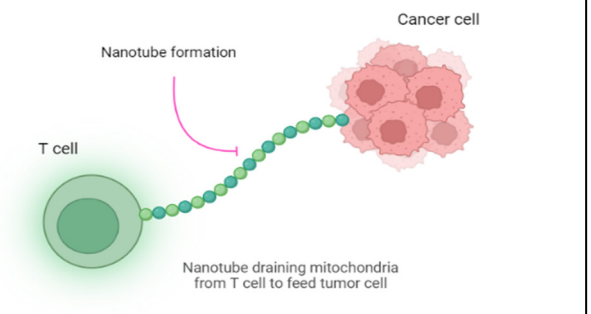

Fig. 4. Nanotube growth weakening T cell [20]
(drawing prepared using BioRender)

Cytokine Therapy
(enhance immune cell function)

Immune cells communicate with each other by direct contact via antigen-receptor pathway. They also communicate with each other by signalling proteins, called cytokines [4]. Cytokines play different roles, such as cell activation to direct immune cells to go to an infection site, cell proliferation to increase the number of immune cells, and cell differentiation to signal to immature cell to develop into specific cell type [21]. For instance, naïve B cells are activated by cytokines released by helper T cells. Only then, does the B cell differentiate into plasma cells which produce antibodies.

Two such cytokines, Interferon-alpha and Interleukin-2 have been approved by FDA for therapeutic use. [1]. The cytokines cause tumor cell death and stimulate immune response, but they come with significant adverse effects, such as cytokine storm or cytokine release syndrome, when the immune system responds too aggressively to immunotherapy [22]. Prompt medical attention is required.

Monoclonal Antibody Therapy
(direct the immune system to cancer cells)

Antibodies have been engineered to bring the immune cells and cancer cells closer to each other to act as connectors [1]. T cell engaging bispecific antibodies have two or more arms with one attaching to the immune cell while the other attaches to the cancer cell [1,23]. Once in close proximity, the T cell is activated and destroys the cancer cell. Several therapeutic treatments have been approved by FDA since 2014 but due to severe side effects they can be administered only in certain facilities that have the proper medical support system [1]. These drugs have been effective for hematologic cancers. There are several ongoing studies for treatment of solid tumor cancers which are more difficult to treat due to the presence of tumor microenvironment (TME), which is immunosuppressive in nature [9]. Further research must address the side effects, which can be increased cytokine release, toxicity as some solid tumor antigens are also present in healthy tissues, infections and tumor-lysis syndrome when tumor cells, on breakdown, release their contents in systemic circulation [23].

Oncolytic Virus Therapy
(virus infects and destroys cancer cells)

Oncolytic virus therapy uses a virus to infect and lyse (destroy) tumor cells [1].

The first FDA approved oncolytic virus therapy was Imlygic, also called called T-VEC (talimogene laherparepvec) [24]. It uses a strain of the cold sore virus (herpes simplex virus) that has been genetically engineered to produce a protein that stimulates the production of immune cells in the body and to reduce the risk of causing herpes [24]. The treatment is injected into tumors. This therapy works by

replicating within tumors and causing the cells to rupture, leading to local inflammation and the release of tumor antigens, which can stimulate an immune response against the cancer [24].

Another oncolytic virus therapy used a modified "Polio" virus that was engineered to selectively infect and kill cancer cells. The poliovirus was genetically altered to prevent it from causing polio and was designed to target and infect cells that expressed high levels of CD155, a receptor commonly found on the surface of many cancer cells [25]. In a Phase 1 trial carried out by Duke University in the USA, an aggressive type of brain cancer (glioblastoma) was injected with the modified poliovirus [26]. The virus infected the cancer cells, replicated within them, causing the cells to burst and die (oncolysis) [26]. This process released tumor antigens into the tumor microenvironment [26]. The release of antigens then stimulated a broader immune response, where the patient's immune system recognized and attacked the remaining cancer cells [26]. The American news channel CBS had covered this study in their renowned "60 minutes" program.

Vaccines

(train to recognize and attack cancer cells)

Cancer vaccines aim to increase the number of "cancer-killing" T-cells. This is done by providing many cancer-specific proteins (cognate antigens) on the surface of tumor cells. After the vaccine with tumor cells is administered, the antigens are transported to the lymph nodes. The B-cells in the lymph nodes are activated to produce antibodies. The T-cells are activated by dendritic cells (DC) which process and present antigen on MHC molecules. The antibodies from B cells and activated effector cells from T cells infiltrate tumors and induce cell death [6].

The different types of cancer vaccines differ in how the conjugate antigens are introduced in the body.

Dendritic Cell Vaccine

DC: dendritic cells are one of many antigen presenting cells (APCs). Dendritic cells (DCs) capture, process, and present antigens to lymphocytes to initiate and regulate the adaptive immune response [5]. DCs are a class of bone - marrow - derived cells found in blood, tissues and lymphoid organs.

The aim of DC vaccine is to introduce specific cancer antigens and use the DCs to process these antigens. DCs can be isolated from the patient's blood or generated in the laboratory [27]. They are then loaded with tumor-specific antigens (TSAs) derived from tumor cells or genetic material, and the loaded DCs are administered back to the patient [27]. The DCs present tumor antigens to CD4+ helper T cells and CD8+ cytotoxic T cells, leading to their activation [27]. The cytotoxic T cells specifically recognize and target cancer cells expressing the tumor antigens, resulting in their elimination [27]. The vaccine also induces a memory response, allowing for a more effective immune response upon subsequent encounters with tumor cells.

Currently, the only approved DC vaccine is Sipuleucel-T (Provenge TM). It was approved by the FDA (U.S.) in 2010 to treat castrate-resistant prostate cancer [6].

Whole Cell Vaccines

Another approach collects cancer cells from the patient's tumor (autologous) or established cancer cell lines (allogenic) [27]. Instead of optimizing a specific antigen to be loaded in DCs (DC vaccine), all antigens associated with the tumor are presented to the immune system [27]. The cancer cells are inactivated or genetically modified (irradiated) to reduce their ability to cause disease [27]. When administered back to the patient, the whole cells are recognized by various immune cells, including DCs, macrophages, and NK cells, triggering an immediate non-specific inflammatory response [27]. The advantage is that the immune system's response is broad involving T cells, B cells and NK cells. Whole-cell cancer vaccines also induce a memory

response for enhanced immune protection against tumor recurrence [27].

Against cancer, Phase I & II clinical trials of various whole-cell tumor vaccines indicate this method is safe for cancer patients. Bacillus of Calmette and Guérin (BCG) vaccine is a main treatment for non-muscle-invasive bladder cancer [1]. For bladder cancer, BCG is given directly into the bladder (intravesical) [28]. This can make the bladder react in a way that makes the immune system get rid of cancer cells [28].

Protein or Peptide Vaccines

These vaccines are made from special proteins in cancer cells, or from small pieces of protein (peptides) leading to highly targeted immune response [29]. Scientists have worked out the genetic codes of many cancer cell proteins, so they can make them in the lab in large quantities. Unlike the DC vaccines that load the antigens inside dendritic cells, ex vivo, peptide vaccines introduce the peptide antigens in the body which are then taken up by APCs (can be DCs) inside the body for processing and presentation to T cells [27]. However, due to their relatively small size, peptides typically have weak immunogenicity and require carrier molecules, delivery carriers or adjuvants (additives to stimulate a stronger immune response) to enhance chemical stability and induce a moderate immune response [29]. Further research areas to realize the full potential of peptide vaccines must address safety issues related to the use of adjuvants and particulate delivery systems [29].

DNA and RNA Vaccines

These vaccines are made with bits of DNA (as plasmids) or RNA (mRNA) which carry the code for the antigenic proteins which will trigger an immune response [6]. Unlike the peptide antigens being introduced in the body (in the case of peptide vaccines), the DNA or mRNA are injected in the skin or muscle [30]. The vaccines use the cellular process of protein synthesis to produce antigenic proteins. In case of DNA vaccines, the target DNA fragment is inserted in a plasmid derived from bacterial cell [6]. The plasmid DNA will translocate to the cell nucleus and be transcribed to mRNA [6]. The mRNA will then translocate back to the cytoplasm, where the antigenic protein will be synthesized by the ribosomes. mRNA vaccines work in a similar way, except the pre-synthesized mRNA is directly injected into the host cells and the cells use their own machinery to translate the mRNA into the target protein antigen [6].

The plasmid DNA must reach the nucleus to work but delivery challenges make the process inefficient [30]. Therefore, DNA vaccines have been found to be effective in small rodents but not in larger animals including humans [30]. DNA can also be degraded by nucleases present in tissues or bloodstream before it reaches the cells and can be degraded within a week [31]. Nano carriers have the advantage of shielding DNA from degradation by enzymes and is an emerging research field [31].

Lipid nanoparticles (LNP) are the preferred carrier of choice for mRNA vaccines as they make their way from the intramuscular injection site to the cell cytoplasm [6]. The LNP also protects the mRNA from degradation by enzymes. When the LNP enters the cytoplasm, they are degraded, thus releasing the mRNA, which is then available to the ribosome for antigenic protein synthesis [6].

DNA and RNA vaccines are not made from live attenuated pathogens, so risk for immune-compromised patients is low. They have the added advantage of being manufactured rapidly and being simple and safe compared to live-attenuated or inactivated vaccines [6]. The Pfizer-BioNTech and Moderna mRNA vaccines were issued an Emergency Use Authorization (EUA) by FDA for Covid-19. The spike protein, which has been shown as the most antigenic SARS-CoV-2 protein, was widely selected as the target of choice for DNA/RNA vaccines and cloned into a plasmid to prepare the vaccine [6]. Recently, the FDA has approved the cancer vaccine, WGc-043 (WestGene), an Epstein-Barr (EB) virus-related mRNA therapeutic cancer vaccine in May 2024, for an investigational new drug (IND) application [32]. The IND application allows the vaccine to be used in

clinical trials with human subjects, which can be significant in the fight against cancers and serve as a positive advancement in cancer treatment [32].

Virus Vaccines

Scientists can genetically modify viruses in the laboratory to either limit or eliminate their replicative ability [33]. The resulting particle, called viral vector, can be used as a type of carrier to deliver cancer antigens into the body without causing the disease normally associated with the virus [33]. The viral protein coat (and envelope) is retained, but the genome inside is inactivated [33].

Most viruses are naturally immunogenic; hence they can be engineered to deliver tumor antigens coded in the modified viral genome (transgene) [34]. The body's immune system will recognize and respond to the cancer antigen expressed by the viral vector. Tumor antigens are more immunogenic when delivered as transgenes in a viral vector, compared to using them as peptide or protein vaccine. [34].

V. CONCLUSIONS

Vaccines represent a promising way in the fight against cancer. However, making vaccine treatments that work pose immense challenges, which is the reason why, despite pioneering vaccine work done by William Coley in 1891 [35], only three therapeutic vaccines were approved by FDA until 2022 [6, 24]. Recent advances in understanding how tumors evade the immune system were crucial in changing the trajectory of cancer therapeutics development. Seminal work by James P. Allison and Tasuku Honjo (Nobel prize in Medicine, 2018), for their discovery of cancer therapy by removing the co-inhibitory signal using antibodies called immune checkpoint inhibitors (ICI) [36], has led to 12 ICI therapeutics approved by US FDA [17,18]. Six CAR-T cell therapies, that provide more cancer-targeted engineered T cells, have been approved for hematologic cancers [36]. They have been less successful with solid tumors; this remains an area of active research. CAR-T cell therapy has severe, potentially life-threatening, side effects which must be understood to expand its use [36]. Seven bispecific antibodies, a type of immunotherapy that can bind to two different targets simultaneously, allowing them to bring immune cells into close proximity with cancer cells, have been approved by the FDA for hematologic cancer and one for solid tumor [37]. There are several active or recruiting clinical trials related to cancer immunotherapy globally, including oncolytic virus therapy, another emerging treatment option. These are exciting times for cancer research, with studies focusing on understanding tumor biology and the tumor microenvironment to develop additional effective treatments and overcoming the severe adverse effects of immunotherapy.

The vast number of research opportunities available in the field of cancer immunotherapy makes a compelling case for aspiring medical researchers to embrace the challenge and carry forward the work of cancer research with the goal of eliminating this formidable disease.

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