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Mini Review

Recent Developments of Vaccines as a Precision Medicine Approach to Cancer Immunotherapy

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Abstract

Precision medicine involves tailoring an individual's genes or proteins to prevent, diagnose, or treat diseases such as cancer. Given the recent advances in cancer immunotherapy, there is now a focus on developing vaccines as a new treatment modality. Therapeutic vaccines for cancer are a precision medicine approach that has made enormous progress in recent years due to advances in vaccine engineering. This technology uses antigens derived from the patient's tumor to create vaccines that are unique and specific to that patient. Although challenges remain, significant progress has been made in recent years, largely due to the advent of mRNA vaccines. This mini-review primarily focuses on developments in vaccine engineering, outstanding therapeutic obstacles, and recent human clinical trials.

Introduction

The field of precision medicine, also referred to as personalized or individualized medicine, is a burgeoning area of research and development, particularly in relation to immunotherapy.[1] Tailoring treatment to a specific patient, rather than using more conventional, broad-spectrum treatments, circumvents many of the side effects associated with traditional approaches. Cancer immunotherapy has emerged at the forefront of this treatment modality, especially with the advent of immune checkpoint inhibitors (ICIs), which have shown significant clinical benefits against several types of cancer.[2] These ICIs are monoclonal antibodies directed against immunosuppressive molecules, such as programmed cell death protein-1, programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte antigen-4.

Precision medicine

Adoptive cell transfer therapy has made enormous progress in cancer immunotherapy in recent years by marshaling and amplifying the body's immune system to fight cancer. Functional immune cells, specifically tumor-infiltrating lymphocytes, which target human leukocyte antigen, are isolated from the patient's tumor, engineered or expanded *ex vivo*, and then readministered to the same patient.[1] This therapeutic modality can be divided into three subtypes: unmodified TILs, chimeric antigen receptor (CAR)-engineered T cells, and T cells with engineered T cell receptor (TCR) fragments.[3]

The most successful form of this treatment modality is CAR T cell therapy. To date, this modality has received six U.S. Food and Drug Administration (FDA) approvals for hematological malignancies.[4] Although this autologous treatment modality has shown considerable success in blood cancers, disadvantages arise from difficulty penetrating solid tumors and factors such as excessive costs, toxic side effects, and lack of tumor-specific antigens. T cells expressing engineered TCR cells represent another therapeutic alternative, as their target repertoire is not limited to membrane proteins. Moreover, intrinsic features such as high antigen sensitivity and near-physiological signaling can improve tumor cell detection and destruction with improved T cell persistence.[5] However, one of the main problems associated with TCR gene therapy is that the engineered T cells cannot distinguish between tumor cells and normal cells expressing target antigens, leading to fatal cardiotoxicity in patients treated for metastatic melanoma.[6]

Natural killer (NK) cell therapy is currently emerging as an attractive option, as it offers several advantages over CAR T cell therapies, including multiple mechanisms of action and reduced alloreactivity. CAR NK therapy also potentially offers an "off-the-shelf" allogeneic product, eliminating the need for a personalized, patient-specific product associated with current CAR T cell therapies.[7] However, drawbacks of this treatment modality include low efficiency of CAR transduction, limited cell expansion, and lack of available targets.[8]

A recent development in this precision medicine approach demonstrated that antitumor T cells in the blood of patients with metastatic solid cancers can be identified and isolated using a newly

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identified signature. Although these cells are sparse, they can now be retrieved without surgery and used to develop personalized cancer immunotherapies.[9] Researchers analyzed T cells using blood from patients with metastatic cancer with T cells from within the tumor, looking for identical receptors. Using single-cell transcriptomic profiling techniques, they identified unique molecular signatures for antitumor T cells in the blood in six of eight blood samples from patients with colorectal cancer, breast cancer, and melanoma. Moreover, the T cells from the blood were found to be less exhausted than the intra-tumor T cells. These cells can potentially be amplified *ex vivo* and re-infused into the same patient. Based on the antitumor results observed in both pre-clinical studies and current human clinical trials, this modality is likely to become a major player in future cancer treatment.[10]

Therapeutic vaccines

Vaccines are biological preparations that elicit an immune response and provide active acquired immunity against a particular infectious or malignant disease. Vaccine immunization is traditionally thought of as a means of preventing disease, as vaccines contain proteins that the immune system recognizes as a pathogen, such as a bacterium or virus, priming the body to respond vigorously in the future. These pathogens possess distinguishing proteins that allow for their recognition. Examples of conventional vaccines include:

Live or attenuated

A weakened form of the pathogen causing the disease elicits a strong and long-lasting immune response. One to two doses can confer lifetime protection against diseases such as measles, mumps, and rubella.

Inactivated

A dead version of the disease-causing pathogen that can lead to higher levels of protection. This type is not as strong as the live version and may require several booster shots.

Toxoid

Utilizes the toxin created by the pathogen instead of the actual pathogen and is used to protect against diphtheria and tetanus. Vaccines are now emerging as a potential treatment modality. Given the enormous strides in design and development in recent years, vaccines are beginning to play a pivotal role in precision medicine.[1] Therapeutic vaccines differ from preventive or prophylactic vaccines, such as measles, and influenza, which protect against future disease, in that they prime a patient's immune system to combat an existing disease.[11]

Therapeutic vaccination for cancer takes advantage of the fact that cancer cells possess distinguishing proteins, or antigens, which differ from normal cells. Although the immune system constantly recognizes and eliminates mutating cells to prevent cancer development, sometimes cancer cells develop mechanisms to evade immune detection. For this reason, there is a current focus on vaccines not as a means of preventing cancer but treating it. Initially, research efforts concentrated on developing vaccines against shared proteins commonly expressed in certain cancers. However, the failure of this strategy in large clinical trials in the mid-2010s has shifted the focus toward personalized approaches.[12]

Personalized cancer vaccines are tailored specifically to individual patients. They work by:

- Eliciting an immune response that results in generating highly specific antibodies against a particular antigen located on the surface of the cancer cell;
- Priming the adaptive immune system to recognize the same antigen on other cancer cells and mount an immune response.

Multiple diseases create mutated proteins that the immune system recognizes as foreign, prompting an immune response. This approach focuses on isolating the target antigen unique to aberrant cells but not normal cells. A piece of surgical tissue (biopsy) is removed from the patient during surgery and genetically analyzed for target tumor-associated antigens or tumor-specific antigens.[13] Vaccines are then generated to target these antigens specifically. Once targeted, the immune system attacks and destroys malignant cells overexpressing these antigens, leading to a long-term therapeutic response due to immunologic memory.[14]

Although enormous progress has been made in recent years with cancer vaccines, considerable hurdles remain. For example, cell-based vaccines are very labor-intensive, and the process of isolating and culturing patient-specific immune cells requires substantial resources and expertise, resulting in high production costs. Additionally, tumors can develop immune evasion mechanisms and create immunosuppressive microenvironments, which include barriers to immune infiltration by anti-cancer immune cells, selective recruitment of immunosuppressive cells, induction of T cell death, production of immunosuppressive enzymes and metabolites, and hypoxic conditions in tumors, all of which can hinder vaccine-induced anti-cancer immune responses.[15] Moreover, high genetic heterogeneity within a tumor, vaccines may recognize the tumor from which they are derived but be ineffective against metastatic tumors.[16]

Vaccine development, from basic research to approval, typically takes about 5 to 10 years.[17] Although a large number of vaccine studies are conducted at the preclinical stage, less than 10% of vaccines are approved. Four types of cancer vaccines are considered specific, safe, and tolerable, and offer attractive therapeutic options (Table 1).[18] A major driver of recent vaccine development is the significant progress made with messenger RNA (mRNA) development.[19,20] The relatively short time required to generate mRNA vaccines that produce specific antigens in an autologous fashion is a major advantage. mRNA vaccines have demonstrated rapid progress and promise as a treatment modality due to their therapeutic effectiveness, low drug resistance, and patient compliance.[21] Moreover, their potential for fast, scalable, and low-cost manufacturing is possible due to the simplicity of mRNA *in vitro* transcription, making it a feasible and safe strategy. Thus, mRNA vaccine development is a highly personalized approach currently under intense investigation, demonstrating efficacy in human clinical trials.

Although cancer vaccines have been researched for over 30 years, few have achieved major clinical success. To date, four therapeutic cancer vaccines have been approved by the FDA and are used to treat different cancers.[22]

- Sipuleucel-T (Provenge®) is used for the treatment of metastatic prostate cancer and is synthesized using patients' own immune cells;
- Bacillus Calmette-Guérin (BCG) is used to treat early-stage bladder cancers and is created from inactivated tuberculosis bacteria;
- Nadofaragene firadenovec (Adstiladrin®) is approved for the treatment of early-stage bladder cancers that are created from an engineered, weakened virus;
- T-VEC (Imlygic®) is an oncolytic virus-based vaccine that is used to treat advanced melanoma that cannot be completely removed with surgery.

Table 1. Cancer vaccine types

Vaccine	Description
Cell-based	Generated normally from either complete cells or cell fragments, resulting in a wide range of tumor antigens, which induce a broad immune response. Examples include dendritic cells (DCs), which have been shown to be effective and safe but are expensive with a complex development process.
Viral vector	Uses a modified version of a virus as a vector that leads to a strong immune response involving both B and T cells. Engineered oncolytic viruses act as vectors capable of presenting high quantities of tumor antigens, resulting in long-term memory, but are also complex to produce.
Peptide-based	Comprised of both chemical or biosynthetic components of known or predicted specific tumor antigen epitopes, these vaccines elicit a strong immune response against specific tumor antigen sites. Although they have formed the basis of hepatitis B and human papillomavirus (HPV) vaccines for liver and cervical cancers, their immunogenicity may be weak due to the small size of the antigen epitopes and major histocompatibility complex (MHC) polymorphisms.
Nucleic acid-based (DNA or messenger RNA (mRNA))	Capable of encoding full-length tumor antigens, which allows APCs to present multiple antigens simultaneously, eliciting strong MHC I-mediated $CD8^+$ T cell responses, resulting in both humoral and cellular immunity. To initiate transcription, DNA vaccines must enter the cell nucleus, whereas mRNA vaccines only require entry to the cytoplasm to allow antigen translation and expression. DNA vaccines carry the potential risk of inserting mutations into the genome, a risk not associated with mRNA vaccines.

APCs, antigen presenting cells.

This landscape has changed in recent years due to some of the aforementioned advances. Additionally, improvements in target identification, formulation, manufacturing and development, combination therapy regimens, and patient selection are showing promise, resulting in around 360 active trials currently ongoing using cancer vaccines.[23] For example, one study reported results from a clinical trial using the VB10.16 vaccine. VB10.16 is a therapeutic vaccine composed of three parts: the first encodes the E6/E7 fusion protein of human papillomavirus (HPV16 E6/7), which plays a key role in developing certain types of cancer; the second comprises a dimerization entity; and the third encodes a protein that specifically binds to antigen-presenting cells. The authors reported that this vaccine was well-tolerated and demonstrated efficacy and strong HPV16-specific T cell responses in patients with high-grade cervical intraepithelial neoplasia.[24]

Another study reported on TG4050, an individualized viral vector vaccine comprising a modified Vaccinia virus Ankara viral vector encoding tumor-specific neoantigens developed using advanced genetic engineering and artificial intelligence technologies. The authors reported that this personalized vaccine was safe, well-tolerated, and induced T cell responses in cold tumors from patients with head and neck carcinoma.[25]

Early clinical trials of mRNA therapeutics include studies of paracrine vascular endothelial growth factor, mRNA for heart failure, and CRISPR-Cas9 mRNA for a congenital liver-specific storage disease.[26] Developing vaccines against cancer is more challenging than against infectious diseases due to the weak immune response and immunosuppressive effects within the tumor microenvironment.[27] However, progress is being made, and several studies are reporting positive results.

A recent publicized result by Moderna of a phase IIb clinical trial reported that a personalized mRNA vaccine (4157/V940) when used in combination with the checkpoint inhibitor pembrolizumab, improved recurrence-free survival compared to pembrolizumab alone in high-risk melanoma patients.[28] The clinical benefit occurred irrespective of the tumor mutational burden. The personalized vaccine, encoding up to 34 patient-specific tumor antigens, was tailored specifically for the patient based on DNA sequences from the tumor and developed over an eight-week period.

Another recently reported phase I clinical trial from Memorial Sloan Kettering Cancer Center used mRNA vaccines directed against the patient's tumor neo-antigens.[29] Tumors were surgically removed from patients, and a vaccine (adjuvant autogene cevumeran) was developed specifically against up to 20 neo-antigens from each patient. Sixteen patients were treated with the anti-PD-L1 antibody atezolizumab and autogene cevumeran, and 15 patients with mFOLFIRINOX alone. Eight of the treated patients generated a strong T cell response to the vaccines, had longer survival, and no reported cancer recurrence 18 months post-treatment. Although the study was small, the results are exciting given the dismal prognosis for pancreatic ductal adenocarcinoma, with a survival rate of 12% after five years. A follow-up phase II trial has opened to build upon this approach to determine its effectiveness.[30]

Strand Therapeutics recently announced FDA clearance for an Investigational New Drug application to initiate a phase 1, first-in-human trial of STX-001.[31] The company claims that their multi-mechanistic programmable mRNA STX-001 expresses cytokine IL12 for an extended period, potentially becoming the first programmable mRNA therapy in oncology. Their platform induces immunogenic cancer cell death in addition to activating and promoting both T cell and NK cell recruitment to the tumor microenvironment. Moreover, the platform also improved the efficacy and durable anti-tumor response when used in combination with checkpoint inhibitors programmed cell death protein-1/PD-L1.

Future directions

mRNA vaccines are rapidly becoming established as a versatile technology for future applications, especially given recent advances. Directly targeting antigens to immune cells has proven to be a successful strategy in developing potent vaccines. For example, dendritic cells are pivotal mediators of both B-cell and T cell immunity. Given their potency as antigen-presenting cells, they are currently the focus of mRNA-delivery systems targeting immune cells for the delivery of cell-specific antigens.[32] Data from clinical trials indicate that personalized mRNA vaccination works as an immune modulator and in a complementary manner with ICIs.[33]

An addition to the mRNA arsenal is self-amplifying RNA (saRNA). saRNA displays several structural similarities to conven-

tional mRNA technology but offers several advantages, including long-lasting effects, lower dosage requirements, and reduced side effects.[34] Positive results have been reported from clinical trials using saRNA technology. Although FDA approval has not yet been granted, the first self-amplifying mRNA vaccine was approved in Japan for a COVID-19 vaccine.[35]

In addition to the advent of mRNA technologies, other technologies are also emerging that show promise as anti-cancer therapies. One such approach involves the administration of engineered inactivated tumor cells to elicit an immune response. In this preclinical study, the authors used CRISPR-Cas9 technology to engineer tumor cells to release interferon beta (IFN-β) and granulocyte-macrophage colony-stimulating factor in a glioblastoma humanized mouse model. The engineered therapeutic tumor cells not only targeted and eliminated the tumors but also improved survival and long-term immunity in primary, recurrent, and metastatic cancer models.[36]

Another recent breakthrough study published in Cancer Discovery reported an innovative approach that identifies key proteins governing both cancer cell metabolism and immune response within tumors. The authors developed BipotentR, a cutting-edge computational tool capable of pinpointing proteins that could disrupt cancer cell metabolism while simultaneously promoting a robust immune response in the tumor microenvironment.[37] Results from both preclinical and clinical models that analyzed gene expression data revealed that BipotentR identified 38 cancer cell-specific immune-metabolic regulators, providing insights into patient outcomes post-immunotherapy. Moreover, artificial intelligence techniques used to assess the activity levels of these regulators within tumors revealed that estrogen-related receptor alpha was highly active in immunotherapy-resistant tumors across various cancer types.

Conclusions

The advent of precision medicine has come to the forefront in recent years, with multiple treatment modalities being applied to several disease indications. In the case of cancer immunotherapy, checkpoint inhibitor blockade has revolutionized the field, leading to dramatic improvements in survival for some patients. However, given that it is not effective in all treated patients, other treatment modalities are required. Central to this effort are mRNA-based vaccines that have either been FDA-approved or are currently under development. Results to date indicate that this personalized treatment offers promising outcomes in the treatment of solid tumors. This technology has been enhanced by advances in mRNA packaging into lipid nanoparticles and polymer biochemistry. Future advances addressing tumor heterogeneity, routes of administration, and efficacy processing will further strengthen this treatment modality. The judicious integration of the aforementioned technologies will likely propel the advancement of mRNA vaccines and immune stimulatory therapeutics for the treatment of multiple clinical indications, including cancer.

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Conflict of interest

JFM is the Founder and President of ImmunePCS LLC. The author declares no other conflict of interests.

Author contributions

JFM is the sole author of the manuscript.

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