ADVANCEMENTS IN CANCER VACCINES: A PROMISING APPROACH FOR CANCER IMMUNOTHERAPY

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Abstract

Cancer remains one of the leading causes of death worldwide, and traditional cancer treatments such as surgery, radiation therapy, and chemotherapy have limitations in terms of efficacy and adverse effects. In recent years, cancer immunotherapy, including cancer vaccines, has emerged as a promising approach for the prevention, treatment, and control of cancer. Cancer vaccines aim to stimulate the immune system to recognize and destroy cancer cells, harnessing the body's own immune response against cancer. In this review article, we provide an overview of cancer vaccines, including the different types of cancer vaccines, their mechanisms of action, and the current status of cancer vaccines in clinical development. We also discuss recent advancements in cancer vaccine research, including the use of novel vaccine platforms, combination therapies, and personalized cancer vaccines. Furthermore, we highlight challenges and future perspectives in the field of cancer vaccines, including the need for standardized clinical trial designs, identification of predictive biomarkers, and improvements in vaccine manufacturing and delivery. Overall, cancer vaccines hold great promise in the field of cancer immunotherapy and have the potential to revolutionize cancer treatment strategies.

Keywords: Cancer vaccines, immunotherapy, cancer immunotherapy, cancer treatment, cancer prevention

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1. Introduction

Cancer continues to be a major global health challenge, with millions of new cases and deaths reported each year (Patel et al. 2022, Singh et al. 2021, Patel and Rajak 2021). Traditional cancer treatments such as surgery, radiation therapy, and chemotherapy have been the mainstay of cancer therapy for decades, but they have limitations in terms of efficacy, toxicities, and resistance (Patel and Rajak 2018, Patel and Rajak 2016)) . In recent years, cancer immunotherapy, including cancer vaccines, has emerged as a promising approach for the prevention, treatment, and control of cancer. Cancer vaccines are a type of immunotherapy that aim to stimulate the immune system to recognize and destroy cancer cells (Cheever 2008, Palucka and Banchereau 2013. They can be categorized into several types based on their targets and mechanisms of action, including preventive vaccines, therapeutic vaccines, and combination vaccines. Preventive cancer vaccines are designed to prevent the development of cancer by targeting infectious agents that are known to cause cancer, such as human papillomavirus (HPV) and hepatitis B virus (HBV). Therapeutic cancer vaccines, on the other hand, are designed to treat existing cancers by stimulating the immune system to attack cancer cells specifically. Combination vaccines, as the name implies, combine multiple cancer antigens or immunomodulatory agents to enhance the immune response against cancer cells (Sharma and Allison 2015, Mellman et al. 2011).

In recent years, significant advancements have been made in the field of cancer vaccines, ranging from the use of novel vaccine platforms, combination therapies, and personalized cancer vaccines. These advancements have shown promising results in preclinical and clinical studies, bringing new hope for cancer patients (Chen and Mellman 2013, Kaufman 2015). In this review article, we will provide an overview of cancer vaccines, including their types, mechanisms of action, and the current status of cancer vaccines in clinical development. We will also discuss recent advancements in cancer vaccine research, challenges, and future perspectives in the field of cancer vaccines.

2. Types of Cancer Vaccines:

Cancer vaccines can be classified into different types based on their targets and mechanisms of action. Here, we provide an overview of types of cancer vaccines:

2.1 Preventive Cancer Vaccines

Preventive cancer vaccines are designed to prevent the development of cancer by targeting infectious agents that are known to cause cancer. These vaccines are typically administered to healthy individuals who are at risk of developing cancer due to exposure to specific pathogens. Examples of preventive cancer vaccines include the HPV vaccine and the HBV vaccine. The HPV vaccine has been shown to be highly effective in preventing HPV infection and related cancers, such as cervical cancer, in both males and females. The HPV vaccine is typically administered to adolescents and young adults, as HPV infection is most commonly acquired through sexual contact. The vaccine targets the viral proteins of HPV, which are responsible for the development of HPV-associated cancers. Clinical trials have demonstrated the safety and efficacy of the HPV vaccine, and it has been widely recommended for routine vaccination in many countries as a part of national immunization programs. Similarly, the HBV vaccine is another example of a preventive cancer vaccine. HBV is a leading cause of liver cancer, and the HBV vaccine has been shown to be highly effective in preventing HBV infection and subsequent liver cancer. The HBV vaccine is typically administered in infancy as a part of routine childhood immunization programs and is also recommended for high-risk individuals, such as healthcare workers and individuals with a history of HBV exposure (Kaufman 2015, Kantoff et al. 2010).

2.2 Therapeutic Cancer Vaccines

Therapeutic cancer vaccines are designed to treat existing cancers by stimulating the immune system to attack cancer cells specifically. These vaccines are typically administered to cancer patients as a part of their treatment regimen. Therapeutic cancer vaccines can target various cancer antigens, including tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), which are expressed on the surface of cancer cells and are not present on normal cells.

One of the promising therapeutic cancer vaccines is Sipuleucel-T (Provenge®), which is approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T is an autologous cellular immunotherapy that involves harvesting the patient's own immune cells, called dendritic cells, which are then exposed to a prostate cancer antigen and re-infused back into the patient. This process stimulates the patient's immune system to mount an immune response against prostate cancer cells. Clinical trials have

shown that Sipuleucel-T improves overall survival in mCRPC patients, making it the first FDA-approved therapeutic cancer vaccine (Kantoff 2010).

Another example of a therapeutic cancer vaccine is the immune checkpoint inhibitors, such as pembrolizumab (Keytruda®) and nivolumab (Opdivo®), which have shown remarkable success in the treatment of various cancers, including melanoma, lung cancer, and bladder cancer. These vaccines work by blocking the proteins on cancer cells that inhibit the immune system, thereby unleashing the immune response against cancer cells. Immune checkpoint inhibitors have shown significant clinical benefits, including durable responses and prolonged survival, in a subset of cancer patients.

2.3 DNA Vaccines

These vaccines deliver fragments of DNA that encode tumor-specific antigens to stimulate an immune response. One examples VGX-3100 vaccine targeting high-grade cervical dysplasia caused by HPV. It contains DNA plasmids encoding antigens specific to HPV types 16 and 18. INO-1400 studied for prostate cancer, this DNA vaccine delivers genetic material encoding prostate-specific antigen (PSA) to elicit an immune response against prostate cancer cells (Trimble 2019).

2.4 RNA Vaccines

These vaccines use RNA molecules to deliver genetic instructions to cells, enabling them to produce specific antigens and trigger an immune response. An example is BNT162b2 (Pfizer-BioNTech COVID-19 vaccine): While primarily developed for COVID-19, it has also been investigated in clinical trials for melanoma and ovarian cancer by delivering mRNA encoding tumor-associated antigens (Sahin 2014).

2.5 Viral Vector Vaccines

These vaccines use modified viruses as carriers (vectors) to deliver tumor-associated antigens to the immune system. An example is Ad26.RSV.preF: Originally developed for preventing respiratory syncytial virus (RSV) infection, it is being investigated as a potential vaccine for lung cancer by incorporating tumor-associated antigens into the viral vector (Roychoudhury et al. 2021).

2.6 Peptide-Based Vaccines

These vaccines use short fragments of proteins called peptides, derived from tumor-associated antigens, to stimulate an immune response. An example is Melacine used for advanced melanoma, this vaccine contains a mixture of peptides derived from melanoma-associated antigens to target melanoma cells specifically (Atkinson et al. 2009).

2.7 Whole Cell/Whole Tumor Cell Vaccines

These vaccines utilize whole tumor cells or whole cell lysates to trigger an immune response against a broad range of tumor-associated antigens. An example is GVAX vaccine is being studied for pancreatic cancer and consists of irradiated pancreatic cancer cells genetically modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), which helps stimulate the immune system (Laheru, 2008).

2.8 Dendritic Cell Vaccines

Dendritic cells play a crucial role in initiating immune responses. In these vaccines, dendritic cells are harvested from the patient, loaded with tumor-specific antigens, and then reinfused to trigger an immune response against the cancer. An example is Provenge (Sipuleucel-T) Approved for advanced prostate cancer, this vaccine is created by collecting a patient's own dendritic cells, exposing them to a prostate cancer-specific antigen, and then reinfusing them to stimulate an immune response against the cancer cells (Kantoff et al, 2010).

2.9 Tumor Antigen-Specific Vaccines

These vaccines target specific tumor antigens to elicit an immune response against cancer cells. An example is: MAGE-A3: Investigated for melanoma and non-small cell lung cancer, this vaccine targeted the MAGE-A3 antigen, which is found in certain tumor cells. However, clinical trials for this vaccine were discontinued (Vander et al. 2016)

2.10 Neoantigen Vaccines

Neoantigens are unique mutations found in individual patients' tumors. Personalized vaccines are created based on these specific neoantigens to trigger an immune response against the patient's cancer cells. An example is GEN-009: Currently in clinical trials for melanoma and non-small cell lung cancer, this personalized vaccine is designed to target patient-specific neoantigens and stimulate an immune response against the tumor (Sahin et al. 2018).

2.11 Viral-Based Vaccines

These vaccines utilize viruses engineered to carry tumor-specific antigens, triggering an immune

response against cancer cells. Adenovirus-based vaccines use adenoviruses as vectors to deliver tumor-specific antigens. They are being investigated for various types of cancer, including lung, prostate, and breast cancer (Sahin et al. 2018).

2.12 Bacterial-Based Vaccines

Some bacteria can be modified to express tumor-specific antigens, serving as vectors to stimulate an immune response. An example is Listeria-based vaccines Listeria monocytogenes bacteria can be engineered to produce tumor antigens, which can activate the immune system against cancer cells. Clinical trials are underway for different types of cancer (Sahin et al. 2018).

2.13 Combination Cancer Vaccines

Combination cancer vaccines are designed to combine multiple cancer antigens or immunomodulatory agents to enhance the immune response against cancer cells. These vaccines aim to overcome the limitations of single-agent vaccines and provide a more effective approach to cancer immunotherapy. One example of a combination cancer vaccine is the use of a prime-boost strategy, where a prime vaccine is administered to stimulate the immune response, followed by a boost vaccine to further enhance the immune response (Sharpe et al. 2018). This approach has shown promising results in preclinical and clinical studies, and several prime-boost vaccine regimens are currently under investigation in clinical trials for various types of cancers. Another example of a combination cancer vaccine is the use of cancer vaccines in combination with other cancer therapies, such as chemotherapy, radiation therapy, or targeted therapies. These combination approaches aim to synergistically enhance the immune response against cancer cells and improve treatment outcomes. For instance, the combination of therapeutic cancer vaccines with immune checkpoint inhibitors has shown promising results in clinical trials, with enhanced antitumor responses observed in some cancer patients (Sachdeva et al. 2020)

Table 1: Type of Vaccine with example

Type of Cancer Vaccine	Example
Preventive/Prophylactic Vaccines	Human papillomavirus (HPV) vaccine (e.g., Gardasil, Cervarix) - Hepatitis B vaccine (e.g., Engerix-B, Recombivax HB)
Therapeutic Vaccines	-Sipuleucel-T (Provenge) for advanced prostate cancer - Oncophage (HSPPC-96) for kidney cancer
DNA Vaccines	-VGX-3100 for high-grade cervical dysplasia associated with HPV - INO-1400 for prostate cancer
RNA Vaccines	-BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) used in clinical trials for melanoma and ovarian cancer
Viral Vector Vaccines	-Ad26.RSV.preF for respiratory syncytial virus (RSV) infection prevention, being investigated for lung cancer
Peptide-Based Vaccines	-Melacine for advanced melanoma
Whole Cell/Whole Tumor Cell Vaccines	-GVAX for pancreatic cancer
Dendritic Cell Vaccines	-Provenge (sipuleucel-T) for advanced prostate cancer
Tumor Antigen-Specific Vaccines	-MAGE-A3 for melanoma and non-small cell lung cancer (discontinued in late-stage clinical trials)
Neoantigen Vaccines	-Personalized vaccines targeting unique mutations in individual patients' tumors, such as GEN-009 in clinical trials for melanoma and non-small cell lung cancer

3. Mechanisms of Action of Cancer Vaccines

The mechanisms of action of cancer vaccines involve the stimulation of the immune system to recognize and attack cancer cells (Wei et al. 2018). Here, we provide an overview of the main mechanisms of action of cancer vaccines:

3.1 Activation of Antigen-Presenting Cells (APCs)

Cancer vaccines often target antigen-presenting cells (APCs), such as dendritic cells, which are crucial for initiating and coordinating the immune response against cancer cells. When cancer vaccines are administered, they stimulate APCs to take up the cancer antigens presented by the vaccine. This results in the activation of APCs, which then present the cancer antigens to T cells, a type of immune cell that plays a key role in destroying cancer cells. The activation of APCs by cancer vaccines helps to prime the immune system and initiate a specific immune response against cancer cells (Sahin et al. 2018, Palucka et al. 2013, Nizard 2020)

3.2 Stimulation of T Cell Response

Cancer vaccines aim to stimulate the immune system to recognize and attack cancer cells. Once the cancer antigens are presented by APCs, they activate T cells, specifically cytotoxic T cells, which are responsible for killing cancer cells. The activated T cells recognize the cancer antigens on the surface of cancer cells and initiate an immune response against them, leading to the destruction of cancer cells (Sahin et al. 2018, Palucka et al. 2013, Nizard 2020).

3.3 Memory Immune Response

Cancer vaccines also induce a memory immune response, which helps the immune system to remember and recognize cancer cells in the future. This is important for long-term protection against cancer recurrence. Once the immune system has been primed by the cancer vaccine, it retains memory T cells that can quickly recognize and respond to cancer cells if they reappear, leading to a more rapid and effective immune response against cancer cells (Chen et al. 2017).

3.4Modulation of the Tumor Microenvironment

The tumor microenvironment refers to the cellular and molecular surroundings of the tumor. It plays a crucial role in tumor growth and immune evasion. Cancer vaccines can modulate the tumor microenvironment to make it less favorable for cancer cells and more conducive to the immune response. For example, some cancer vaccines can stimulate the production of cytokines, which are signaling molecules that promote immune cell infiltration into the tumor, or inhibit the production of immunosuppressive molecules by cancer cells, leading to an enhanced immune response against cancer cells (Sahin et al. 2018, Palucka et al. 2013, Nizard 2020).

4. Combination with Other Cancer Therapies

As mentioned earlier, cancer vaccines can be combined with other cancer therapies, such as chemotherapy, radiation therapy, or targeted therapies, to enhance their overall effectiveness. For example, chemotherapy or radiation therapy can help to debulk the tumor, which can then be followed by a cancer vaccine to stimulate the immune response against the remaining cancer cells. Additionally, targeted therapies that specifically target cancer cells can help to sensitize the tumor to the immune response induced by the cancer vaccine, leading to improved treatment outcomes (Ribas 2018).

5. Clinical Trials and Efficacy of Cancer Vaccines

Numerous clinical trials have been conducted to evaluate the safety and efficacy of cancer vaccines in different types of cancers. While the results have been variable, some cancer vaccines have shown promising outcomes in specific cancers. Here, we provide an overview of the clinical trials and efficacy of cancer vaccines in various cancer types:

5.1 Prostate Cancer

Sipuleucel-T (Provenge®), a therapeutic cancer vaccine, has been approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) based on the results of the pivotal Phase III clinical trial called IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment). In this trial, Sipuleucel-T showed a statistically significant improvement in overall survival compared to placebo, with a median overall survival of 25.8 months in the Sipuleucel-T group compared to 21.7 months in the placebo group. Sipuleucel-T has been shown to be well-tolerated with manageable side effects, such as chills, fever, and fatigue.

5.2 Melanoma

Melanoma is a type of skin cancer that has been a focus of cancer vaccine research. The FDA has approved the use of the cancer vaccine talimogene laherparepvec (T VEC, or T-VEC, marketed as Imlygic®) for the treatment of unresectable melanoma lesions that cannot be completely removed by surgery. T-VEC is an oncolytic virus-based cancer vaccine that is injected directly into the melanoma lesions, where it replicates and destroys cancer cells, while also stimulating an immune response against cancer cells. The Phase III clinical trial of T-VEC, called OPTiM (Oncovex Pivotal Trial in Melanoma), showed a significant improvement in durable response rate compared to the control group, with an overall response rate of 16.3% in the T-VEC group compared to 2.1% in the control group. T-VEC has shown a favorable safety profile with manageable side effects, including flu-like symptoms and injection site reactions (Kim et. al., 2019).

5.3 Lung Cancer

Lung cancer is a leading cause of cancer-related deaths worldwide, and the development of effective cancer vaccines for lung cancer has been challenging. However, several clinical trials have been conducted to evaluate the efficacy of cancer vaccines in lung cancer. One example is the Phase

III clinical trial of the cancer vaccine belagenpumatucel-L (Lucanix®) in patients with stage III/IV non-small cell lung cancer (NSCLC). Although the trial did not meet its primary endpoint of overall survival, a subgroup analysis showed that patients who received belagenpumatucel-L had a significantly longer median survival time compared to the control group. Another example is the Phase III clinical trial of the cancer vaccine racotumomab (Vaxira®) in patients with advanced NSCLC, which showed a significant improvement in overall survival compared to placebo. Further research is ongoing to develop more effective cancer vaccines for lung cancer (Gandhi et. al. 2018).

5.4 Colorectal Cancer

Colorectal cancer is another common type of cancer that has been targeted by cancer vaccines. The cancer vaccine, known as GVAX, which is derived from two human colon cancer cell lines genetically modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), has been evaluated in clinical trials for the treatment of advanced colorectal cancer. Phase II clinical trials have shown promising results with improved overall survival in patients who received GVAX in combination with chemotherapy compared to chemotherapy alone. However, further research is needed to establish the efficacy of GVAX as a cancer vaccine for colorectal cancer.

5.5 Breast Cancer

Breast cancer is a heterogeneous disease with various subtypes, and the development of effective cancer vaccines for breast cancer has been challenging. However, several cancer vaccines targeting breast cancer-associated antigens, such as HER2/neu and MUC1, have been evaluated in clinical trials. For example, the cancer vaccine NeuVax® targets HER2/neu, a protein that is overexpressed in approximately 20-30% of breast cancers. Phase II clinical trials of NeuVax® in patients with HER2-positive breast cancer have shown promising results, with improved disease-free survival in vaccinated patients compared to the control group. Further research is ongoing to develop more effective cancer vaccines for breast cancer.

Table 2: Clinical Status of Cancer Vaccine

Vaccine	Cancer Type	Clinical Trials	Efficacy
Gardasil	HPV-related cancers	Phase III trials have shown effectiveness in preventing cervical, vaginal, vulvar, and anal cancers caused by HPV.	High efficacy in preventing HPV infections and related cancers.
Provenge	Prostate cancer	Phase III trials demonstrated improved overall survival in advanced prostate cancer patients.	Increased overall survival with a modest improvement in median survival.
Oncophage (HSPPC-96)	Kidney cancer	Phase II trials showed improved overall survival in patients with metastatic renal cell carcinoma.	Increased overall survival and long-term durable responses observed in some patients.
Sipuleucel-T	Prostate cancer	Phase III trials demonstrated a survival benefit in metastatic castration-resistant prostate cancer.	Extended overall survival, but modest improvement in median survival.
MAGE-A3	Melanoma and lung cancer	Phase III trials in melanoma and non-small cell lung cancer were discontinued due to lack of efficacy.	Not proven effective in improving survival or preventing cancer recurrence.
BNT162b2 (Pfizer-BioNTech COVID-19 vaccine)	Melanoma and ovarian cancer (investigational)	Clinical trials investigating the vaccine's efficacy in melanoma and ovarian cancer are underway.	Efficacy data specific to cancer treatment not available yet.
GVAX	Pancreatic cancer	Phase II trials demonstrated improved overall survival in advanced pancreatic cancer patients.	Increased overall survival and improved immune response observed in some patients.
GEN-009	Melanoma and non-small cell lung cancer (investigational)	Clinical trials evaluating the vaccine's efficacy in melanoma and non-small cell lung cancer are ongoing.	Efficacy data specific to cancer treatment not available yet.
Ad26.RSV.preF	Lung cancer (investigational)	Clinical trials investigating the vaccine's potential in lung cancer are ongoing.	Efficacy data specific to cancer treatment not available yet.
INO-1400	Prostate cancer	Phase I/II trials are assessing the vaccine's safety and efficacy in prostate cancer patients.	Efficacy data specific to cancer treatment not available yet.

6. Safety and Adverse Effects of Cancer Vaccines

Overall, cancer vaccines have been shown to be well-tolerated with manageable side effects. Common side effects of cancer vaccines include flu-like symptoms such as fever, chills, and fatigue, as well as injection site reactions, such as pain, redness, and swelling. These side effects are generally mild to moderate in severity and resolve on their own without any specific treatment. In some cases, cancer vaccines may also cause more serious adverse effects, such as allergic reactions, although these are rare. As with any medical intervention, it is important to carefully evaluate the safety profile of cancer vaccines in clinical trials and monitor for adverse effects in real-world clinical practice (Sharma and Allison 2015).

7. Future Directions and Challenges

While cancer vaccines have shown promising results in clinical trials for certain types of cancer, there are still challenges that need to be addressed in order to further improve their efficacy and bring them into widespread clinical use. Some of the key future directions and challenges in the field of cancer vaccines include:

Identification of effective cancer antigens: One of the key challenges in the development of cancer vaccines is the identification of appropriate cancer antigens that can stimulate a specific immune response against cancer cells without harming normal cells. Not all cancer cells express the same antigens, and the selection of the right antigens for a specific cancer type is crucial for the success of a cancer vaccine. Further research is needed to identify novel cancer antigens that can be targeted by cancer vaccines (Nishino et. al. 2016).

Personalized cancer vaccines: Cancer is a highly heterogeneous disease, and each patient's tumor has unique genetic mutations and antigen expression patterns. Personalized cancer vaccines, which are tailored to the individual patient's tumor, have shown promising results in preclinical and early clinical studies. However, the development and implementation of personalized cancer vaccines pose challenges in terms of cost, logistics, and regulatory approval. Further research is needed to optimize the development and delivery of personalized cancer vaccines (Mellman et. al. 2011).

Combination therapies: Cancer vaccines have shown synergistic effects when used in combination with other cancer treatments, such as chemotherapy, radiation therapy, and immune checkpoint inhibitors. Combination therapies can enhance the efficacy of cancer vaccines by targeting cancer cells from multiple angles and overcoming immune evasion mechanisms. However, the optimal timing, sequence, and dosing of combination therapies need to be carefully evaluated in clinical trials to achieve the best outcomes.

Immune-related adverse effects: Cancer vaccines work by stimulating the immune system, and as such, can sometimes cause immune-related adverse effects, such as autoimmune reactions or immune-mediated toxicities. The management of immune-related adverse effects is an important consideration in the development and clinical use of cancer vaccines, and further research is needed to better understand and manage these adverse effects.

Access and affordability: Cancer vaccines, like other cancer treatments, can be costly, and access to these treatments may be limited in certain regions or populations. Ensuring affordability and accessibility of cancer vaccines to all patients who may benefit from them is an important consideration for their widespread use. Strategies such as pricing models, reimbursement policies, and global collaborations are needed to address these challenges (Jürgensmeier et al. 2015).

8. Conclusion

Cancer vaccines have emerged as a promising approach in the field of cancer immunotherapy, offering the potential to harness the body's immune system to target and destroy cancer cells. Over the years, significant progress has been made in the development of cancer vaccines, with several vaccines showing promising results in clinical trials for various types of cancer. The FDA approval of Sipuleucel-T and T-VEC for the treatment of prostate cancer and melanoma, respectively, has further validated the potential of cancer vaccines as a viable treatment option for cancer patients. However, challenges still remain, and further research is needed to optimize the efficacy, safety, and accessibility of cancer vaccines. Identifying effective cancer antigens, developing personalized cancer vaccines, exploring combination therapies, managing immune-related adverse effects, and addressing issues of access and affordability are some of the key areas that require further attention in the field of cancer vaccines. Despite these challenges, cancer vaccines hold great promise as a complementary approach to conventional cancer treatments, offering the potential for durable and

targeted anti-cancer responses. With continued research and innovation, cancer vaccines have the potential to revolutionize cancer treatment and improve outcomes for cancer patients.

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