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A Review on Cancer Vaccines: A New Frontier in Immunotherapy and Precision Oncology

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Abstract: *Cancer vaccines represent a groundbreaking approach in oncology, aiming to train the immune system to recognize and attack tumor-specific antigens, thereby providing a targeted and potentially long-lasting therapeutic effect. Over the past four decades, extensive research has explored various cancer vaccine strategies, yet their successful clinical translation remains a challenge due to several biological, technical, and logistical barriers. This review delves into the landscape of 360 clinical trials investigating different vaccine modalities, including peptide-based, dendritic cell (DC), RNA, DNA, and viral vector-based vaccines, each with distinct mechanisms, advantages, and limitations. Among these, peptide vaccines have garnered the most attention, comprising 34.2% of trials, particularly for cancers such as melanoma, lung, brain, and breast cancer. While peptide-based vaccines are relatively simple to manufacture and customize, their clinical efficacy is often constrained, necessitating the use of combination therapies to enhance immune response and overcome tumor evasion mechanisms. Similarly, DNA and RNA vaccines have gained momentum with the advent of advanced computational antigen prediction, personalized sequencing, and improved delivery technologies, positioning them as promising candidates for precision oncology. However, the path to clinical success is fraught with hurdles, including immune system suppression by tumors, manufacturing complexities, regulatory challenges, and ethical considerations associated with certain vaccine technologies. Furthermore, despite the theoretical advantages of cancer vaccines, their integration into mainstream oncology is hindered by inconsistent patient responses, the requirement for highly individualized treatment strategies, and the need for robust immune system activation to achieve sustained antitumor effects. This review critically examines these challenges while highlighting recent innovations that have the potential to reshape the field of cancer immunotherapy. As scientific advancements continue to refine antigen selection, vaccine formulation, and delivery methods, cancer vaccines hold the promise of becoming a vital component of multimodal cancer treatment strategies, especially when combined with immune checkpoint inhibitors, chemotherapy, and other emerging therapeutic approaches. By addressing the existing limitations and leveraging cutting-edge technologies, cancer vaccines could ultimately bridge the gap between preclinical potential and clinical efficacy, paving the way for a new era in cancer treatment.*

Keywords: Cancer Immunotherapy, Tumor-Specific Antigens, Peptide and RNA Vaccines, Immune Evasion Mechanisms, Precision Oncology

I. INTRODUCTION

Cancer is a group of linked disorders that can arise practically anywhere in the body, rather than a single illness. Cancer is essentially a genetic disease that affects our body's cells. Our cells are controlled by our genes. However, alterations to these genes can lead to abnormal cell behavior, either by stopping cells from dying when they should or by causing them to grow and divide when they should not. These aberrant cells may develop into cancer. With trillions of cells making up the human body, cancer can begin practically anywhere. Human cells typically divide to create new cells as needed by the body by growing and multiplying. New cells replace old ones when they die because of aging or injury. This controlled mechanism can occasionally malfunction, causing damaged or aberrant cells to proliferate and expand when they should not. Tumors are lumps of tissue that can be formed by these cells. Cancerous or benign tumors can

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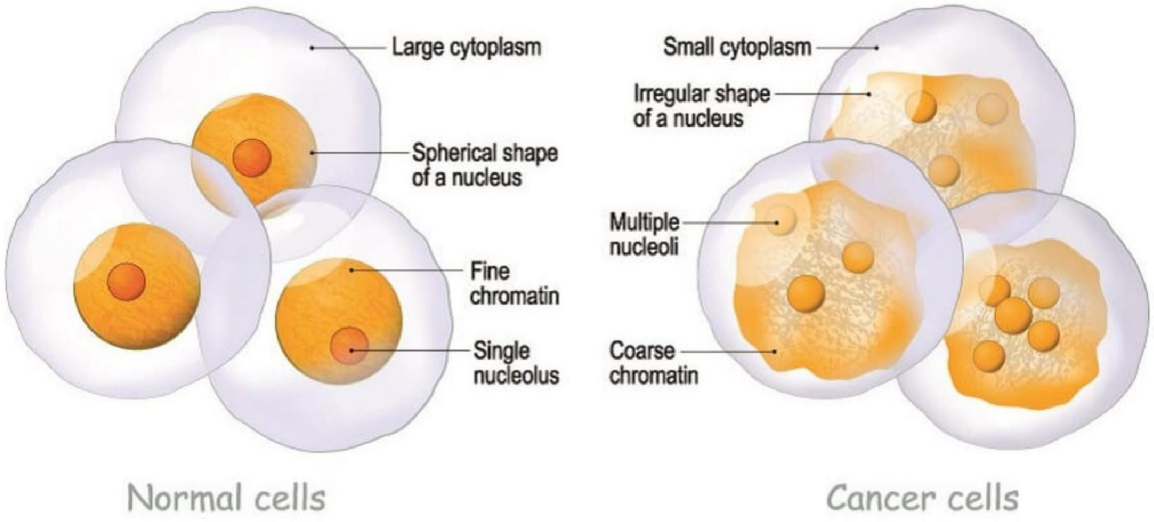
both occur. Malignant tumors can metastasize, or spread into, neigh boring tissues, and can also generate new tumors by traveling to far-off regions of the body.[1]

Normal cells and **cancer cells** are not the same in many aspects. As an example, cancer cells: •proliferate when they do not receive signals to do so. Only in response to these cues do normal cells proliferate.

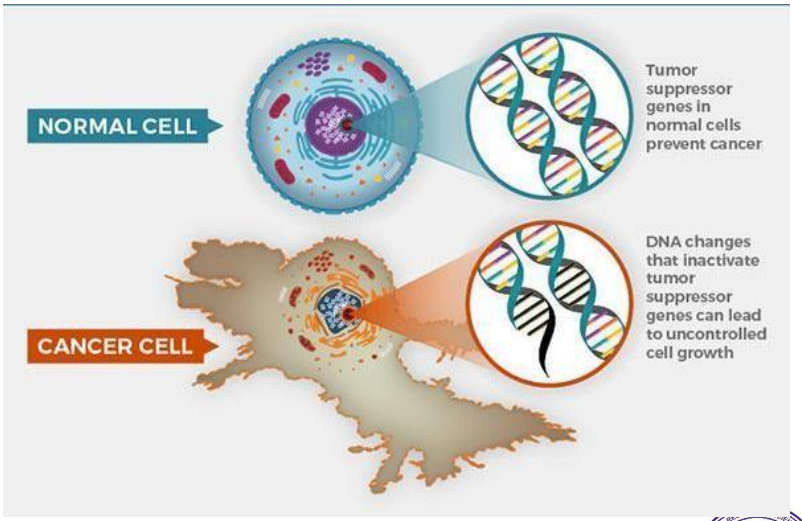
- Direct blood vessel growth in the direction of malignancies. These blood veins remove waste materials from tumors and provide oxygen and nutrition to the tumors.
- Evade the body's defenses. Damaged or aberrant cells are typically eliminated by the immune system.
- A mass a variety of chromosomal modifications, including chromosomal duplications and deletions. Some cancer cells have twice as many chromosomes as healthy cells.[1]



Since cancer is a hereditary disease, it results from alterations to the genes that regulate how our cells behave, particularly how they divide and proliferate.

Errors that arise during cell division can result in genetic alterations that lead to cancer. of DNA damage brought on by dangerous environmental factors, like the toxins in cigarette smoke and the sun's UV radiation. (For further information, see our section on Cancer Causes and Prevention.)

they were inherited from our parents.[1]



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Not all changes in the body's tissues indicate the presence of cancer. However, some tissue changes have the potential to develop into cancer if left untreated, For instance.

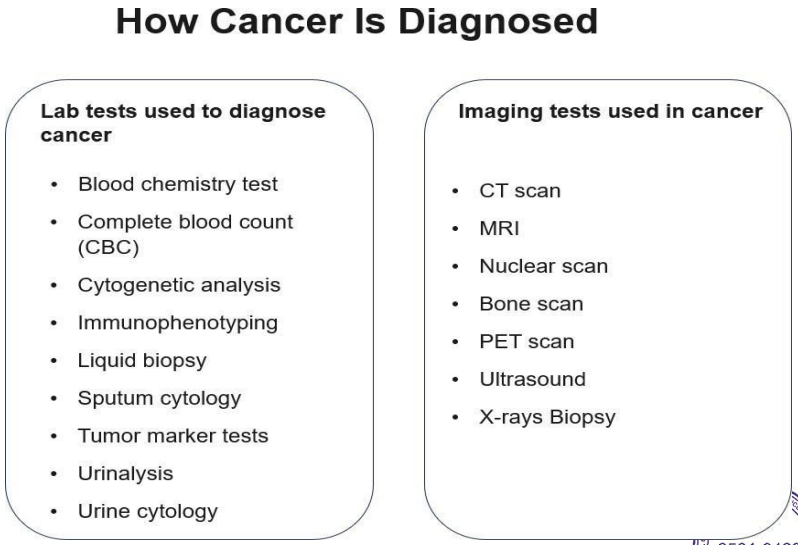
- **Hyperplasia** occurs when cells in a tissue multiply at a faster rate than normal, resulting in an accumulation of extra cells.
- **Dysplasia**, on the other hand, is a more advanced condition than hyperplasia, where abnormal- looking cells accumulate and there are alterations in the organization of the tissue.
- **Carcinoma in situ** represents a more progressed state. Despite being referred to as stage 0 cancer at times, it does not qualify as cancer since the abnormal cells do not infiltrate neigh boring tissue like cancer cells do. However, given the potential for some carcinomas in situ to develop into cancer, they are typically addressed through treatment. [1]

Statistics at a Glance: The Burden of Cancer in the United States

- It is predicted that in 2024, there will be 2,001,140 new cases of cancer diagnosed in the US, and 611,720 deaths from the illness.
- In 2024, colorectal, lung, and prostate cancers will be responsible for 48% of all cancer diagnoses in men. Breast, lung, and colorectal cancers are the three most common cancers in women; by 2024, they will be responsible for 51% of all new cancer diagnoses in this population.
- Based on cases from 2017 to 2021, the annual rate of new cases of cancer, or cancer incidence, is 440.5 per 100,000 men and women.
- Based on deaths from 2018 to 2022, the cancer death rate, or cancer mortality, is 146.0 per 100,000 men and women annually.[1][2]

Common Cancer Types :

- Breast Cancer
- Bladder Cancer
- Pancreatic Cancer
- Kidney (Renal Cell) Cancer
- Lymphoma
- Colorectal Cancer
- Lung Cancer
- Skin Cancer
- Prostate Cancer
- Uterine Cancer



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Vaccine:

In oncology, vaccines represent a vitally important public health intervention that have not yet attained historic clinical efficacy. Due to certain antigens' aberrant overexpression or unique expression on tumor cells, vaccination has potential as a therapeutic approach. Thus, a cancer vaccine aims to train the immune system of a patient to identify and combat cancerous cells. For forty years, there has been extensive clinical research on cancer vaccines, but the field has seen very few successes in very specific circumstances. Immunotherapy has always been a desirable and possibly effective cancer treatment in this setting. There are two types of tumor immunotherapy: (a) passive (or adaptive), which involves giving cells or antibodies outside of the body, and (b) active, which includes vaccines and is intended to trigger a particular immune response against tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). [1][2]

Type of cancer vaccine	Nature/composition	Advantages/disadvantages
Whole-cell tumor vaccine	Attenuated whole cancer cells derived from a patient.	Cheap and highly immunogenic. Autologous or allogenic.
Antigen based vaccines	Sub-unit vaccines composed of ell characterized antigens/epitopes.	No patient specificity. Offer the advantage of multiantigenicity. Synthesis may be challenging.
Dendritic-cell vaccines	Sub-unit vaccines composed of autologous immune-cells that have been converted to DCs.	Highly immunogenic. Patient specific. Highly expensive.
DNA-vaccines	Sub-unit vaccines composed of vec-tors transfected with bits of DNA.	Sustained immune response. No immune supression.
Virus-like particle (VLP) based vaccines	Sub-unit vaccines composed of VLPs derived from various HPV types.	Very effective against HPV type 6, 11, 16 and 18.

CLINICAL LANDSCAPE AND METHODOLOGY :

The current study examined 360 cancer vaccine trials in total. The trial space as of July 2022 is reflected in the data. We removed trials that did not meet the criteria for a vaccine, those with indications other than cancer, and those that had been underway for more than ten years without disclosing anticipated outcomes were among the irrelevant listings we removed from the original pool of trials. Tumor antigens were defined for the purposes of this study as being present in or encoded by cancer vaccines. In situ vaccines were the only exception; they had to be specifically marked as such in the trial listing and were searched specifically for them. Vaccines intended to stop malignancies in remission from returning were included in the general study but were not classified as preventive. 142 cellular (37.7%) and 235 soluble (62.3%) vaccines were among the 377 unique vaccine interventions that we found, broken down by trial, out of the 360 trials that were examined. Peptide vaccines were the most prevalent single category overall (123/377, or 32.6%) and made up more than half of the soluble vaccine space (123/235, or 52.3%). The second most often studied vaccines are DC vaccines, which make up most of the extensive FIGURE 2 Summary of the current state of cancer vaccine clinical trials. the most common indications broken down by organ/anatomic site; (b) the phases of 360 clinical trials; (c) the landscape of antigen classifications; (e) the percentage of trials that used a combination therapy (top right bar); and (f) the combination therapies by category, among trials that used a combination.

Antibody, combination, antigen-presenting cell, dendritic cell, immune checkpoint blockade, N/A, not applicable, and Ab, antibody NC, not in conjunction; Phase is denoted by Ph, small molecule by SM, tumor-associated antigen (TAA) by TSA. 5 of 24 23806761, 2024, 1, JANES ET AL. retrieved on [25/09/2024] from https://aiche.onlinelibrary.wiley.com/doi/10.1002/btm2.10588, Wiley Online Library. For usage guidelines, visit Wiley Online Library's Terms and Conditions https://onlinelibrary.wiley.com/terms-and-conditions; OA articles are subject to the applicable Creative Commons License. They include a significant portion of the cancer vaccine space (28.7%) and the vast

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majority of the cellular vaccine space (108/142, 76.1%). DC vaccines were followed by viral (10.9%), DNA (6.9%), RNA (6.1%), and tumor cell (5.8%) vaccines. The bulk of trials (68.9%) are at Phase 1 or 1/2, with Phase 2 (27.5%) and Phase 2/3 and 3 (7 trials, 1.7%), following. This indicates the challenge of clinical advancement in the field as well as the abundance of new products that are still undergoing clinical trials.[1][3]

CURRENT CLINICAL TRIALS :

1. Peptide vaccines

Peptide-based cancer vaccines are attractive because they can be personalized, are easy and quick to manufacture, and are relatively inexpensive. Of all vaccine modalities, these vaccines are used in the greatest number of ongoing clinical trials—124,360 (34.2%). Cancers that arise in a variety of target sites are treated with peptide-based vaccines, the most common being the brain (15%), lung (12%), breast (10%), and skin (8%). Since the primary goal of peptide vaccines is to load endogenous APCs with tumor antigens in order to initiate cellular immune responses, proper maturation of APCs is essential to vaccine efficacy.[3][4]

Surprisingly, an adjuvant was not specifically mentioned in 38.8% of peptide-based vaccination studies. Both adjuvants are widely tolerated and reasonably priced. Vaccines are most frequently administered via subcutaneous (SC) (65.5%) and intradermal (ID) (25.3%) routes among trials with a specified administration route. While peptides injected ID may drain to lymph nodes or be absorbed and processed by dermal APCs, peptides injected SC are anticipated to drain to lymph nodes for absorption and antigen processing. The majority of peptide-based vaccinations (54.1%) target tumor associated antigens (TAAs). Of the 30 Phase 2 trials identified, 24 (80%) target TAAs, with the most common targets being hTERT (23%) and HER2 (13%). Thirty-four neoantigen trials are in Phases 1 and 1/2 (37% of all Phase 1 and 1/2 trials), and two are in Phase 2 (7% of all Phase 2 trials). Neoantigen targets were mentioned 36 times (29.5%). This discrepancy most likely results from more recent developments in small-batch production, computational antigen prediction, and customized sequencing. As these obstacles to antigen identification continue to disappear, neoantigen-targeting peptide-based vaccines may see rapid clinical development.

It is interesting to note that just 25 trials (20.7%) use peptide-based vaccines as single treatments. Combining vaccines with ICB (44.5%), chemotherapy (20.3%), and cytokine therapy (21.9%) is the most common practice. Although chemotherapy and ICB may work in concert with vaccination to reduce tumor burden, these figures also probably consider the fact that peptide vaccines are rarely effective enough to be used as monotherapies.[4]

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TABLE 1 Examples of current clinical trials for peptide cancer vaccines.

NCT	Phase	Sponsor/ collaborator	Product name	Indication	Antigen type	Antigens	Adjuvants	Route	Combination therapy	Specific combination	Extra details	Other trials
NCT02358187	2	Ian F Pollock	GAA/TT	Pediatric low-grade glioma	TAA	GAA	PolyICLC	SC	N/A	N/A	Tetanus toxoid conjugate	N/A
NCT04930783	1	Dana Farber Cancer Institute, Celldex Therapeutics	NeoVax	Advanced melanoma	Neoantigen	N/A	PolyICLC	SC	Antibody-ICB, cytokine	Nivolumab, CDX-301	Long neoantigen peptides	NCT03929029, NCT02287428, NCT03361852, NCT03219450, NCT02950766, NCT04024878
NCT04580771	2	MD Anderson Cancer Center	PDS0101	Cervical cancer	Viral	HPV E6, E7	N/A	SC	Chemotherapy	Cisplatin	Delivered via liposome	N/A
NCT04382664	2	Ultimovacs ASA	UV1	Melanoma	TAA	hTERT	N/A	ID	Antibody-ICB, cytokine	Nivolumab, ipilimumab, GM-CSF	N/A	NCT04300244, NCT04046445, NCT03538314, NCT05075122, NCT01784913, NCT01789099
NCT02960230	1/2	Sabine Mueller	H3.3K27M	Diffuse intrinsic pontine glioma	TSA	H3.3K27M	Montanide ISA 51 VG, tetanus toxoid, polyICLC	SC	Antibody-ICB	Nivolumab	N/A	N/A
NCT02654587	3	OSE Immunotherapeutics	OSE2101	Non-small cell lung cancer	TAA	CEA, HER2, MAGE2, MAGE3, P53, PADRE	N/A	SC	N/A	N/A	N/A	NCT04713514

Abbreviations: HPV, human papillomavirus; ICB, immune checkpoint blockade; ID, intradermal; TAA, tumor-associated antigen; TSA, tumor-specific antigen; SC, subcutaneous.

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II. RNA VACCINES

Clinical trials for RNA cancer vaccines are moving quickly thanks to two significant technological developments: [4][6]

1. Creation and verification of drug delivery vehicles for in vivo RNA protection.
2. Advances in computer programs to find immunogenic epitopes for successful neoantigen vaccinations.

RNA vaccines are currently being used in 23 trials, or 6.4% of all 360 trials. It is anticipated that this figure will rise sharply in the upcoming years. In four of these trials, a viral vaccine is combined with a heterologous prime-boost strategy.[7][8]

RNA Vaccine Targets:

- **Neoantigens**: Most common target (45% of trials).
- **Tumor-Associated Antigens (TAAs)**: Second most common (30% of trials).
- **Tumor-Specific Antigens (TSAs)**: Includes shared KRAS mutants.
- **Viral Targets**: HPV in two trials.
- **Total Tumor RNA**: Derived from tumor lysate in two trials.

Lipid-Based Carriers:

- **Lipoplexes**: Used by BioNTech and Stamina, consisting of cationic lipids that self- assemble with mRNA.
- **Liposomes**: Have a lipid bilayer surrounding an aqueous phase with encapsulated cargo.
- **Lipid Nanoparticles (LNPs)**: Used by Moderna, containing a lipid core stabilized by surfactants.

Injection Routes:

- **Intravenous (IV)**: Most common route.
- **Intramuscular (IM) and Intradermal (ID)**: Shown to promote more persistent antigen expression.

BioNTech's Lipoplex Vaccines:

Demonstrate tropism for secondary lymphoid organs and bone marrow, facilitating dendritic cell uptake and a strong immune response.

- **Indications and Trials**: There are 19 RNA therapeutic trials for solid tumors. The three Phase 2 trials include one for head and neck squamous cell carcinoma (HNSCC) (NCT04534205) and two for melanoma (NCT03897881, NCT04526899).
- **Corporate Sponsorship**: 87% (20 out of 23) of RNA trials have corporate sponsors, likely due to the high costs of RNA therapeutic development. BioNTech SE is involved in 8 trials, and Moderna in 2.
- **Moderna's mRNA-4157**: This lead candidate is a lipid nanoparticle encapsulating mRNA encoding up to 20 patient-specific neoantigen sequences. It is administered intramuscularly (IM) with the anti-PD-1 antibody pembrolizumab in trials for melanoma (NCT03897881) and multiple solid tumors (NCT03313778).

Efficacy Milestone: In the KEYNOTE study (NCT03897881), mRNA-4157 achieved its primary goal towards the end of 2022. improving recurrence-free survival in completely resected melanoma compared to checkpoint blockade alone. This success highlights advancements in LNP formulation, neoantigen prediction, RNA structural optimization, combination therapy synergy, and patient selection.[9][10][11]

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TABLE 2 Examples of current clinical trials for RNA cancer vaccines.

NCT	Phase	Sponsor/ collaborator	Product name	Indication	Delivery vehicle	Antigen type	Antigens	Route	Combination therapy	Specific combination	Other trials
NCT03897881	2	Moderna	mRNA-4157	Melanoma (resected)	Lipid nanoparticle	Neoantigen	N/A	IM	Antibody-ICB	Pembrolizumab	NCT03313778
NCT04526899	2	BioNTech SE	BNT111	Melanoma (checkpoint refractory/ unresectable)	Lipoplex	TAA	NY-ESO-1, MAGE-A3, tyrosinase, TPTE	IV	Antibody-ICB	Cemiplimab	N/A
NCT03418480	1/2	University of Southampton, BioNTech SE	HARE-40	Head and neck, cervical, anogenital	Lipoplex	Viral	HPV E6, E7	ID	Antibody-agonist	Anti-CD40	N/A
NCT04573140	1	University of Florida	RNA-LP	Glioblastoma	Liposome (DOTAP)	Lysate (autologous), viral	TTRNA from lysate, pp65-LAMP	IV	Radiation	N/A	N/A
NCT04534205	2	BioNTech SE	BNT113	Head and neck squamous cell carcinoma	Lipoplex	Viral	HPV E6, E7	IV	Antibody-ICB	Pembrolizumab	N/A
NCT04382898	1/2	BioNTech SE	BNT112	Prostate cancer (metastatic, castration-resistant)	Lipoplex	TAA	PAP, PSA, and three undisclosed	IV	Antibody-ICB	Cemiplimab	N/A

Abbreviations: HPV, human papillomavirus; ICB, immune checkpoint blockade; ID, intradermal; IM, intramuscular; IV, intravenous; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; TAA, tumor-associated antigen; TTRNA, total tumor RNA.

III. DNA CANCER VACCINES

DNA vaccines work by introducing tumor antigens and other costimulatory factors into the injection site cells, which in turn triggers an immune response. This analysis identified 20 trials that used a DNA approach only. Plasmids serve as the antigen delivery vehicle in all of these trials, and many of them use multiple plasmids to encode various adjuvants, cytokines, and antigens.[14]

Administration Routes:

- Intradermal (ID): 13 trials
- Intramuscular (IM): 8 trials
- Unspecified: 1 trial

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Enhancement Techniques:

Electroporation is a widely used technique that can increase intracellular gene delivery by up to 1000 times, thereby increasing immunogenicity.

Common Indications:

- Breast cancer: 18.9%
- Anogenital cancers: 13.5%
- Prostate cancer: 10.8%
- Lung cancer: 10.8%

Clinical Trial Phases:

- No ongoing Phase 3 trials
- 40% of the trials (8 out of 20) are in Phase 2

Examples of DNA Vaccines:

1. **WOKVAC:** This treatment regimen includes ID chemotherapy and targeted therapy, and it encodes three tumor-associated antigens (TAAs) (NCT04329065, NCT02780401). IL-12 and the E6 and E7 viral antigens linked to HPV16/18 are expressed by three plasmids that make up INO- 311
2. **Durvalumab** (NCT03439085), an immune checkpoint antibody, is also administered intraperitoneally (IM). Six out of ten patients in a Phase 1 cervical cancer trial produced a T cell response that was detectable using ELISpot.

- **DNA vaccine antigens:** most DNA vaccines express tumor-associated antigens (TAAs), with HER2 being the most prevalent, particularly in trials pertaining to breast cancer. Certain vaccines employ neoantigens in a tailored manner.
- **VB10.Neo:** This DNA vaccine containing up to 40 neoantigens was created by Nykode Therapeutics and licensed to Genentech. It targets antigen-presenting cells (APCs) with the help of CCL3
- **Combination Approaches:** Combination therapies account for 85% of trials. Immunocheckpoint blockade is the most often used combination, followed by chemotherapy and cytokines such as IL- 2 and GMCSF. [14][15]

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TABLE 3 Examples of current clinical trials for DNA vaccines.

NCT	Phase	Sponsor/ Collaborator	Product name	Indication	Antigen type	Antigens	Route	Combination therapy	Specific combination	Extra details	Other trials
NCT04329065	2	University of Washington	WOKVAC	Breast cancer	TAA	HER2, IGF-1R, IGFBP2	ID	Antibody-targeted, chemotherapy	Trastuzumab, pertuzumab, paclitaxel	N/A	NCT02780401
NCT03548467	2	Nykode Therapeutics	VB10.Neo	Skin, lung, kidney, urothelial, head and neck	Neoantigen	N/A	IM	Cytokine	Bempegaldesleukin	CCL3-tagged neoantigens	NCT05018273
NCT03287427	1	Peter MacCallum Cancer Centre	TetMYB	Colorectal, salivary gland	TAA	MYB	ID	Antibody-ICB	Tislelizumab	Antigen fused to tetanus toxoid	N/A
NCT03600350	2	University of Wisconsin, Madison	pTVG-HP	Prostate (non-metastatic)	TAA	PAP	ID	Antibody-ICB, cytokine	Nivolumab, GM-CSF	N/A	NCT02499835, NCT04090528

Abbreviations: ICB, immune checkpoint blockade; ID, intradermal; IM, intramuscular; GM-CSF, granulocyte-macrophage colony-stimulating factor; TAA, tumor-associated antigen.

IV. VIRAL AND HETEROLOGOUS VACCINES

Heterologous prime-boost approaches, in which antigens are delivered using two distinct viral vectors, frequently employ viral vaccines. By promoting T cell proliferation that is specific to the antigen, this technique helps prevent secondary immune responses to the viral vector itself. Overview of Trials: Of the 38 trials that were found, 28 (73.7%) employ a combination strategy using two distinct vectors. Among them are: 18 dual viruses, 4 viruses/RNA, 4 viruses/yeast, 1 virus/protein, and 1 virus/DNA • Phases of Trials: o Twelve trials (31.6%) are at Phase 2; one trial is at Phase 2/3 • Gritstone Bio: Gritstone Bio is registered for all four viral/RNA approaches. Their flagship product combination, GRT-C901 and GRT-R902, delivers the boosting dose via liposome- delivered self-amplifying mRNA and the priming dose via a chimpanzee adenoviral vector. With encouraging results from a Phase 1/2 trial (GRANITE), they are now conducting their most advanced trial, a Phase 2/3 trial for metastatic colorectal cancer (NCT05141721). Of the nine patients in this trial, four exhibited a molecular response, and their median survival was more than 18 months, while the non-responders' median survival was 7.8 months. As of the last report, the median overall survival (OS) had not yet been reached.[17]

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Target Antigens:

The majority of viral trials (60.5%) focus on antigens associated with tumors (TAAs). o Neoantigens are the focus of some trials (18.4%). o Heterologous prime-boost strategies that target various antigen types are used in a few trials.

Viral Scaffolds:

Adenovirus type 5, fowlpox, and chimpanzee adenovirus are examples of common viral scaffolds.

Example - BN-Brachyury Vaccine:

Aims to target the TAA brachyury in prostate cancer. Uses multiple boosting doses with a fowlpox vector and two subcutaneous priming doses with an MVA vector. The TAA brachyury and three T cell costimulatory molecules—B7-1, ICAM-1, and LFA-3—are encoded in both vectors. T cell and NK cell activation, as well as systemic cytokine production, are enhanced by intravenous administration. Results of the phase 1 experiment showed that 9 out of 13 patients had a T cell response to brachyury, while 7 out of 11 patients developed CD8 T cell responses to CEA and MUC1.

Indications:

Gastric/esophageal junction (11.4%), colorectal (11.4%), and prostate (12.9%) cancers are common indications for viral-based cancer vaccines.

Therapeutic Combinations:

In 89.5% of trials, a therapeutic combination is used. o Common interventions include chemotherapy, immune checkpoint blockade (ICB) (368.8%), antibody blocking, and cytokines. o Bintrafusp alfa (targets TGF-β and PD-L1) and bevacizumab (targets VEGF) are examples of blocking antibodies

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TABLE 4 Examples of current clinical trials for viral and heterologous vaccines.

NCT	Phase	Sponsor/ Collaborator	Product name	Indication	Het.?	Primary construct	Secondary construct	Antigen type	Antigens	Route	Combination therapy	Specific combination	Other Trials
NCT05141721	2/3	Gritstone Bio	GRT-C901, GRT-R902	Colorectal cancer	Yes	Chimpanzee adenovirus	Self-amplifying mRNA, via liposome	Neoantigen	N/A	IM, IM	Chemotherapy, antibody-targeted, antibody-ICB	Oxaliplatin, fluoropyrimidine, bevacizumab, ipilimumab, atezolizumab	NCT03639714, NCT05456165
NCT05445882	2	National Cancer Institute	BN-brachyury	Prostate cancer	Yes	Modified vaccinia Ankara (MVA)	Fowlpox	TAA	Brachyury (w/ costim. factors B7-1, ICAM-1, LFA-3)	SC	Cytokine, antibody-blocking	N-803, bintrafusp alfa	NCT03493945
NCT03632941	2	Duke University	VRP-HER2	Breast cancer (recurrent or refractory)	No	Alphavirus-like replicon particles, derived from VEE virus	N/A	TAA	HER2	IM	Antibody-ICB	Pembrolizumab	N/A
NCT04990479	1	Nouscom SRL	Nous-PEV	Melanoma, non-small cell lung cancer	Yes	Great ape adenovirus (GAd)	Modified vaccinia Ankara (MVA)	Neoantigen	N/A	IM	Antibody-ICB	Pembrolizumab	N/A

Abbreviations: costim, costimulatory; Het, heterologous, ICB, immune checkpoint blockade; IM, intramuscular; mRNA, messenger RNA; SC, subcutaneous; TAA, tumor-associated antigen; TSA, tumor-specific antigen; VEE, Venezuelan equine encephalitis.

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V. TUMOR CELL VACCINES :

Among the first cancer vaccines tested on humans were those based on tumor cells. Still, they only represent 5.3% (19/360) of all trials that have been identified thus far. Of all the modalities, tumor cell-based approaches are the most homogeneous because GVAX, a cellular vaccine that has been the subject of extensive clinical evaluation for decades, was used in all identified trials. In order to produce GM-CSF, a cytokine that attracts and activates APCs, autologous or allogeneic tumor cells are usually transduced with an adenovirus. The tumor cells are then lethally irradiated to stop the tumor cells from proliferating inside the patient.

Genetically modified tumor cells are used in all 19 trials; 15 of these (78.9%) express GMCSF. Every reported route is either SC or ID injected. Thirteen trials (68.4%) use off-the-shelf allogeneic cells, while six trials (31.6%) use autologous cells from patient biopsy material. Eight out of the nineteen trials that were found to be relevant are for pancreatic cancer. Furthermore, none of the trials are listed at Phase 3, but 8/19 are listed at Phase 2. Out of all the trials, 12/19 (63.2%) employ a combination approach, with ICB (29.2%) and chemotherapy (41.7%) being the most often used interventions. Chemotherapies are frequently the standard of care for these patients, making them crucial for the ethical design of clinical trials. Additionally, ICB may be able to lessen the exhaustion of T cells that are specific to antigens generated by vaccines.[18]

Limitations of Cancer Vaccines :

Cell-based Vaccines:

- High production costs due to patient-specific immune cell isolation and culturing.
- Challenges in mass production and distribution.
- Tumor microenvironments can suppress immune cells, reducing efficacy.
- Immune evasion by tumors hinders vaccine effectiveness.
- Logistical challenges in transportation and storage.[18]

iPSC-based Vaccines:

- Ethical concerns over the use of embryonic stem cells and genetic manipulation.
- Risk of tumor formation or unwanted cellular responses.
- Potential for immune evasion reduces anti-tumor immune response.[19]

In Situ Vaccines:

- Difficulty in identifying tumor-specific antigens in genetically heterogeneous cancers.
- Tumor microenvironment may suppress immune responses.
- Limited effectiveness against metastatic tumors.[20]

Microbial Vector Vaccines:

- Pre-existing immunity to viral vectors reduces effectiveness.
- Safety concerns with certain microbial vectors.
- Limited cargo capacity restricts delivery of multiple tumor antigens.[21]

Nucleic-acid-based Vaccines:

- Requires specialized delivery systems for DNA/RNA transfection.
- Transient antigen expression may need multiple doses.
- Risk of immune tolerance reduces long-term efficacy.[22]

Peptide-based Vaccines:

- Focus on specific tumor antigens may lead to overlooked mutations, limiting their effectiveness.
- May overlook other relevant tumor antigens, limiting the comprehensive immune response.
- Depend on binding to specific HLA molecules, restricting use to patients with compatible HLA types.

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- Genetic diversity of tumors complicates efficacy, as some tumor cells may lack targeted peptides.[23]

II. CONCLUSION

The analysis that follows highlights the varied and dynamic field of cancer vaccines. Cellular (DC/APC) vaccines, tumor cells, peptides, RNA, DNA, and viral vectors are the primary vaccine types under investigation. The type of vaccine, combination therapies, patient-specific factors, antigen selection, and indications all have a significant influence on the clinical responses that cancer vaccines produce. Our assessment of ongoing clinical trials suggests that paying careful attention to each of these variables will be critical to the future success of cancer vaccines. Many promising preclinical interventions, such as new adjuvants and drug delivery vehicles, are not yet included in the current analysis because it frequently takes years for cancer vaccine trials to move from one clinical phase to the next. Despite the disappointing clinical outcomes to date, the most recent data suggest that vaccines may have a more permanent place in the growing array of therapeutic interventions.

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