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THE LANDSCAPE OF THERAPEUTIC CANCER VACCINE

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ABSTRACT: Cancer vaccines, a unique approach to cancer therapy are the propitious tools in the hands of the clinical oncologist. Immunization with these specific cancer vaccines put forth an antitumor effect by captivating the host immune response, and has immense prospective for avoiding the inherent drug resistance that confines typical cancer management. Strategies to attain affirmative clinical consequences are entrusted better with the combination of these cancer vaccines with the most effectual immunotherapy agents. Advantages recline as they have exquisite specificity, low toxicity, and the prospective for a robust treatment outcome due to immunologic memory. A handful of propitious prophylactic vaccines are found to be more flourishing in cancer deterrence, still the progress of effective cancer vaccines demand for continued efforts, thoughtful clinical trials, and scientific progress for effective and long-term specific cancer vaccines.

INTRODUCTION: Cancer, a major pernicious disease has been one of the notable causes of destruction in evolved and advancing countries. A surprise intensifying rise in malignancy has been scrutinized beside the significant advancement in the recent years (new targeted therapies) where current occurrences of cancers are projected to rise from 11.3 million in 2007 to 15.5 million in 2030. Comparably cases of cancer death have been estimated to increase from 7.9 million in 2007 to 11.5 million towards 2030. [1-3] Cancer, a mass of cell growth is unconfined and autonomous which occupy the adjoining tissue thereby replacing the inhabitant cells ensuing in promulgating disease and finally death. [4]

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Cancer frequency and pervasiveness influenced by the factors as demographic reposition in the population approaching older ages, use of tobacco and other stuffs, advances in screening and identification, communicable agents, and embracing of the western lifestyle by mounting nations.[5]

The existing accessible management effort to optimize the cancer includes the techniques as Surgical resection, transplantation, local ablation therapies, chemotherapy, gene therapy, laser therapy, radio therapy, stem cell therapy and angiogenesis blockers respectively. Still the on hand approaches attach with limitations as they appear to be very toxic, develop resistance and further can mess up the quality of life with due course of time.[6-8]

Diverse approaches trailed in cancer vaccines (immunology) to tackle the power of cancer patient's (immune system) which proof highly fetching and unconventional loom against tumor

cells. In today's contemporary medication immunization revitalizes up to avert acute infections disease as beneficial cancer vaccines stimulate the immune system to identify antigens and strike specific cancer cells without destroying the normal cells. Eradication of the malignant cells and trimming down of the auxiliary development of accessible tumor cells ensues in condensed reappearance and augmentation of the survival rate with the use of the cancer vaccines. [9-11]

The basis of this present assessment focus on the exertion involved in the progress of different types of cancer vaccines and the prospective behind the progression taken to improve the overall specificity against cancer anticipation and treatment for future investigation.

Spectrum of cancer vaccines: [12, 13]

Preventive/prophylactic vaccines:

They are deliberate to prevent cancer from developing in healthy people.

Therapeutic/treatment vaccines:

They are anticipated to serve on an existing cancer by nourishing the body's natural defenses against the cancer.

Specific Cancer Vaccines:

They are anticipated to treat specific type of cancers where different vaccines are needed to treat different types of cancers.

Universal Cancer Vaccines:

They exert to withstand against cancer cells irrespective of cancer type.

Vaccine Modalities:

A. Protein-based vaccine- Antigen vaccine, Anti-Idiotype antibody based vaccine.

B. Cellular-based vaccine- Tumor cell vaccine, Dendritic cell vaccine.

C. Vector-based vaccine- DNA vaccine, Viral-vector based vaccine.

Antigen vaccines: [14, 15]

These antigen vaccines are habitually proteins/peptides based vaccine which endorse tumor specific antigens. Further these antigens act in the tumor vicinity of the patient whereby body's immune system furnishes an increasing amount of antibodies (T lymphocytes). Ideally the molecules confined as the antigens should be diverse between normal and tumor cells to clinch its specificity which will mark the tumor cells rather than the normal cells. Provocation persists to prevail over definite level of immune tolerance and designing of appropriate vaccine. Henceforth, most antigens vaccine for cancer is procured from mutated or modified self-protein which confirmed to have an assured level of immune tolerance.

Anti-Idiotype antibody based vaccine: [16, 17]

Experts believe that antibodies opposed to other antibodies are salient in helping to retain the immune system in authenticating. Anti-idiotype antibody based vaccine (contemplate like the antigen and non-native), while countering with the body causes the immune system to charge the anti-idiotypes along with the antigens themselves. Investigators assess the most propitious targets for anti-idiotype vaccines as lymphomas vaccines because it hold unique antigen receptors which is not opt to be adjacent in normal lymphocytes or other normal cells of the body. Further knowing of the best anti-idiotype antibody which will function as a true surrogate antigen for tumor-associated antigens system is the supreme challenge of immunotherapy for the researchers to generate ideally both humoral and cellular immune response.

Tumor cell vaccine: [17-19]

These cellular based tumor cell vaccines (allogeneic/autologous) have been scrutinized for many years in both preclinical models and in clinical trials in humans for the efficacy. The cancerous cell from any individuals are treated in the lab in convinced ways as by radiation, chemicals, genes, tumor lysates (fragments of destroyed tumor cells), tumor oncolysates (an extract made from cancer cells infected with a strain of virus destructive to the cancer cells), apoptotic bodies (fragments of cells that have died a natural death), transduced tumor cells (cancer cells that have been altered through genetic engineering), etc to enhance the likelihood to notice as foreign substance by the immune system. Further these cells while countering with the body,

the immune system recall antigens on these cells, which incriminate to pursue out and attacks any other cells with these antigens that are still in the body. Adjuvants (Aluminium salts/alum, oil-in-water emulsion, monophosphoryl lipid) tend to fortify the work of vaccine better as by increasing the immune system response. The capability of these vaccines extends by blending it to dendritic cells with the hope of invigorating the immune system.

Dendritic cell vaccine: [20, 21, 17]

Cellular based dendritic cell vaccines contemplate the antigen presenting cells (APC) of the immune system to identify cancerous cell and are inimitable in their potential to invigorate T cells. Being an autologous vaccine, the approach used to generate them is tricky and lavish. Experts adopt blending of tumor antigens with dendritic cells in diverse forms which are being conveyed to many patients in order to conflict unwieldy disease, abolish micro-metastatic disease, and afford a reminiscence mechanism to fight tumor reappearance. Numerous cellular based dendritic cell vaccine have been developed which encompass as tumor peptides/whole proteins, mRNA/DNA tumor derived, viral vectors (retroviruses) transduced, lentiviruses, adenoviruses, fowl pox, alphaviruses, whole necrotic or apoptotic tumor cells, tumor cell lysates and dendritic cell fused with tumor cells respectively. Still provocation persists in specifying the unsurpassed dendritic cell vaccine from several subsets and demand to delineate a uniform decorum with curtailing the time and cost necessities respectively.

DNA vaccine: [22-27]

Vector-based DNA vaccines depended on bacterial plasmid assembles to afford a steady supply of antigens to maintain the immune response obtainable hereby articulating the disease-specific antigen via promoter elements and consequent cell transfection that are dynamic in mammalian cells. Plasmid DNA vaccines act via two ways as the antigen encoded by the plasmid is assembled in host cells, either in professional antigen presenting cells (APCs) leading to direct priming of immune responses or in nonprofessional cells from where they can be transferred to APCs leading to cross-priming. Also, as DNA plasmids are obtained from bacteria, it can excite the innate immune system by interacting with toll-like receptor respectively. The vital approach employed for augmenting the DNA vaccine potency can be achieved by physical methods (Gene gun, ultrasound, electroporation, tattooing, and laser) and viral/non-viral delivery systems (viral vectors, cationic lipids/liposomes, micro/nano particles, cationic peptides/cell-penetrating peptides, polysaccharides and cationic polymers) respectively.

Major advantages lies in as due to its simplicity of production, reasonable and purified, do not require any unique management or storage conditions. The lone drawback of DNA vaccines (mainly if using oncogenic DNA) is the potential of the DNA to integrate into the genome of the cell that takes it up, thus promoting malignancy. Using RNA instead, an added current loom, can evade the integration problem.

Viral-vector based vaccine:

Vector-based viral vaccines have been examined with the tendency to express proteins from foreign pathogens, further inducing unambiguous immunological responses against the antigens *in vivo*. These vaccines are self-adjuvant which can deliver more than one cancer antigen at a time possibly to increase a response by the immune system. But the disadvantage lies that with repeated use, host-induced antibodies can neutralize the vector thereby limiting its efficacy. [28, 29] Development of vector-based viral vaccine named as Vaccinia [30] (Poxvirus) long 20 years ago further extended with the modified Vaccinia virus Ankara (MVA), [31] avian poxviruses (fowl pox, [32] canary pox [33, 34]). The probability of combination of viral vector-based vaccine with other vaccines modalities gives an added benefit. The optimal activation of the antigen presenting cells can be imitated as a natural infection by these vaccines.

Combination with additional therapies:

Cancer vaccination although possess potential loom but its combination with additional therapies (surgery, chemo, radiation, and some forms of targeted therapy) could produce much more synergistic effects. [35] The efficiency of cancer treatment vaccines may augment with the surgical removal of large tumor masses making it easier for

the body to develop an immune response as data suggests. [36] The prospect for the growth of combination therapies involving vaccines in the nearby future will direct us as how greatest to exercise a specific cancer treatment vaccine with the vision of the answers in clinical trials by researchers.

Cancer vaccine side effects:

The probable side effects of cancer vaccines reported comprise a skin reaction at the injection site, a skin rash or mild flu-like symptoms, fever, chills, weakness, dizziness, nausea or vomiting, muscle ache, fatigue, and headache. Certain cancer vaccines may cause more specific symptoms. In analogous to traditional system of vaccines, hereby vaccines anticipated to treat cancer emerge to have a safety measure. [37]

Approved Cancer Vaccines: [38]

Gardasil (Merck & Co.), a human papillomavirus quadrivalent recombinant vaccine (Types 6, 11, 16, and 18) is use for the prevention of certain strains of human papillomavirus (HPV). Gardasil is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the diseases (cervical, vulvar, vaginal, and anal cancer, genital warts) caused by Human Papillomavirus (HPV) types included in the vaccine. It is also indicated in boys and men 9 through 26 years of age for the prevention of the diseases (anal cancer, genital warts and anal intraepithelial neoplasia) caused by HPV types included in the vaccine.

Cervarix, a human papillomavirus bivalent recombinant vaccine act against certain types of cancer-causing human papillomavirus (HPV). It is designed to prevent infection from HPV types 16 and 18, which cause about 70% of cervical cancer cases. These types also cause most HPV-induced genital and head and neck cancers. It is approved for use in females 9 through 25 years of age.

Sipuleucel-T (Provenge/APC8015) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer.

Oncophage, a modified cancer vaccine expected to be used in patients with renal cell carcinoma (a type of kidney cancer) that had not yet spread to other parts of the body (localised), brain cancer, metastatic melanoma, and renal cancer. It was designated as an 'orphan medicine' for renal cell carcinoma.

New cancer vaccines candidates which are presently under clinical trials are as follows. [39-42]

Vaccine approach	Vaccine developer (product)	Status
Hormone resistant prostate cancer	Onyvax (Onyvax-P)	Phase-II
Metastatic melanoma with at least one tumor to create vaccine	Avax Technologies (M-Vax)	Phase-III
AML in remission	Geron (GRNVAC1)	Phase-II
Colorectal cancer	IDM Pharma (Collidem)	Phase-I
Hormone-dependent, nonmetastatic prostate cancer	Northwest Biotherapeutics (DC-Vax Prostate)	Phase-III
Advanced NSCLC	NovaRx (Lucanix)	Phase-III
Stage III NSCLC	Oncothyreon (Stimuvax)	Phase-III
Melanoma	Norwood Immunology (Melanoma cancer vaccine)	Phase-II
Glioblastoma multiforme	CellDex (CDX-110)	Phase-II/III
Advanced-stage melanoma	Cytos Biotechnology (CYT004-MelQbG10)	Phase-II
Node-negative breast cancer	Generex Biotechnology (IiKey/HER2/neu cancer vaccine)	Phase-II
Metastatic pancreatic cancer	Cell Genesys (GVAX pancreatic)	Phase-II
Melanoma targeting MAGE-A3	Glaxo Smith Kline	Phase-III
Solid tumors	NY-ESO-1	Phase-I
HER2-expressing tumors	HER2 vaccine	Phase-I
Targets CEA antigen associated with stage 3 colorectal cancer	AVX701 vaccine	Phase-I

CONCLUSION AND FUTURE PERSPECTIVES:

To fight with the most terrible disease around the world, researchers participate as a commendable approach for cancer vaccines. It symbolizes as a promising type of biological therapy for a wide variety of cancer types which is still typically investigational. A consequential range of recombinant vaccines is in hand for exercise yet achievement with these vaccines is inadequate. Challenges revoke as many people with cancer have abridged immunity and consequently their immune systems are not able to respond to the vaccines. Also, some tumors producing proteins and chemicals prevent the immune system from attacking effectively, even when it has been enthused by vaccine. Hence, call for an appropriate preclinical and clinical study is indispensable to further assess the approaches and the capability of these vaccines to extend survival pace in patients with early stage disease needs to be investigated. The decisive purpose of vaccine-based cancer immunotherapy is to draw a persuasive immune response that will grounds the abolition of the tumor as well as create a long-term memory response that will assurance entire remission and keep the cancer in verify.

Future advancement and progress in this vicinity will certainly offer the human mankind striking weapons to battle with all kind of cancers with continuous efforts, clinical trials, and scientific advancement.

CONFLICT OF INTEREST STATEMENT:

The author does not declare any conflict of interest.

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