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## Cancer Vaccines: History, Recent Breakthroughs and Commercial Perspectives

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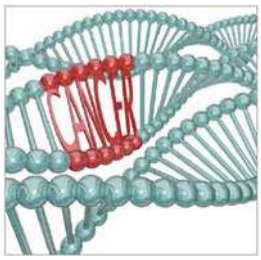


Despite advances in the understanding of cancer biology, improvements in surgical techniques and radiotherapy, new therapeutic agents and targeted therapies, long term survival remains an issue and better, less toxic treatments are needed. Cancer vaccines with the potential for ease of administration and low side effects are a theoretically appealing form of treatment when compared with that of standard cytotoxic chemotherapy. However, several obstacles need to be overcome before vaccines can be utilized for cancer treatment. Whilst this article will focus on lung cancer, the key points can essentially be applied to all other forms of cancer.

For a cancer to progress to a clinically detectable level, it has to evade the immune system and overcome the host's "immunosurveillance". Vaccination must, therefore, be able to induce an effective cellular or humoral immune response capable of tumour destruction, an immune response that has not occurred naturally, despite the presence of foreign tumour antigens. Therefore, the use of adjuvants to augment the anti-cancer immune response becomes of key importance. A second problem is that of choosing a target for vaccination. Ideally, vaccine antigens that are targeted are unique to cancer cells thereby avoiding the risk of the vaccine causing autoimmunity. Over the last 5 years considerable advances have occurred in the understanding of cancer biology, with it now being evident that many different genetic abnormalities and many different "driver mutations", may be present in similar forms of cancer. This is particularly so in lung cancer, which is the most common cause of cancer mortality and one of the most difficult to treat cancers with the poorest outcomes.

Most of the cancer vaccines in development and in clinical trials are considered therapeutic vaccines, as they are designed for administration to patients already diagnosed with cancer. To date, there are two marketed therapeutic cancer vaccines, the Provenge vaccine approved by the FDA, for prostate cancer and the other a lung cancer vaccine approved by the Cuban regulatory authority (see below). However, about 900 cancer vaccines are currently in various stages of clinical trials. Whilst the results of many previous cancer vaccines trials have been disappointing, several recent approaches have shown promise and are discussed below.

***Cancer Vaccines Already in Clinical Use***

**Provenge Prostate Cancer Vaccine**

Currently the only cancer vaccine approved for use in the USA is Provenge, (Sipuleucel-T), used to treat asymptomatic or minimally-symptomatic metastatic, hormone-resistant, prostate cancer. Provenge treatment requires extraction of the patient's own blood cells (antigen presenting cells) by leukapheresis, incubation of these cells with the antigen prostatic acid phosphatase (PAP) (present in 95% of prostate cancer cells) and granulocyte-macrophage colony stimulating factor, and re-infusion of the PAP-labelled blood cells cells in to the patient. Clinical trials suggested that Provenge is able to improve life expectancy in advanced disease, by an average of 4 to 7 months. The side effects of Provenge were mostly limited to chills, fever, fatigue, nausea and headache which usually occurred within the first few days of treatment. Although this strategy demonstrates the effectiveness of cancer vaccines, it would be difficult to apply to lung cancer given that, unlike prostate cancer, lung cancer lacks a universal antigen such as PAP. Overall, Provenge has not been a major commercial success, with factors including the complexity of its preparation and its extremely high cost to the patient.

**Cuban EGFR-targeted Lung Cancer Vaccine**

The Epidermal Growth Factor Receptor (EGFR) is over-expressed in many forms of lung cancer. Moreover, mutations of the EGFR which may lead to excessive activation are found in 15% of Non-Small Cell Lung Cancer (NSCLC) in Caucasian populations. Researchers based at the Centre of Molecular Immunology in Havana, Cuba, have developed a vaccine targeting the EGFR, called CimaVax-EGF. In randomized studies of patients with locally advanced and metastatic NSCLC, treated with initial cytotoxic chemotherapy, this vaccine has been associated with improved survival and was well tolerated with only modest side effects (fever, malaise and myalgia at the time of injection). Currently this vaccine is accepted as standard of care in Cuba although further studies to better define the extent of response and optimal regime of chemotherapy are currently underway in Cuba and other centres.

**Lung Cancer Vaccine Trials**

The MUC1 gene is part of a group of genes that are responsible for the coding of mucin glycoproteins that are strongly expressed in a large number of different tumour types. MUC1 is suspected to enhance tumour progression and contribute to immunosuppression and in patients with lung cancer; expression of MUC1 is associated with poor prognosis. L-BLP25 (Stimuvax) is a liposome-based cancer vaccine that targets the exposed core peptide of MUC1. It consists of a 25-amino acid sequence specific to MUC1, monophosphoryl lipid A (a non-specific immune stimulant), and a liposomal delivery system. This vaccine is intended to target MUC1 and induce a cellular immune response against neoplastic tissue that expresses the MUC1 antigen. A Phase IIB trial was conducted in patients with late stage lung cancer who had responded or who were stable after first-line chemotherapy or chemo-radiotherapy. The median survival time was 17.4 months for patients in the L-BLP25 arm, compared to 13 months for patients in the best supportive care arm. The overall safety and efficacy of this vaccine and its effect on survival will be tested in an upcoming Phase III trial.

TG4010 is a suspension of recombinant Modified Vaccinia virus, containing coding sequences for human MUC1 antigen and human

Interleukin-2 (IL-2), and is meant to induce both innate and adaptive immune responses. A Phase IIB trial assessed the effectiveness of this vaccine in combination with cisplatin/gemcitabine chemotherapy in patients with locally advanced or metastatic NSCLC expressing MUC1 by immunohistochemistry, and with good performance status. There was an increased response rate and improved progression free survival in the combined treatment group compared with that of the group treated with chemotherapy alone, suggesting that TG4010 enhances the effect of chemotherapy in advanced NSCLC. However, patients in the vaccine treated group did have an increased incidence of fever, abdominal pain and injection-site pain. Post-hoc analysis suggested that a subgroup of patients with normal levels of activated Natural Killer (NK) cells at baseline analysis achieved a more marked response. Confirmatory Phase IIB / III trials are currently underway.

Belagenpumatucel-L is a non-viral, gene-based, allogeneic tumour cell vaccine. It consists of 4 lung cancer cell lines. An open label, three-arm, randomized phase II study of low medium and high dose showed that patients who received high doses showed a greater survival advantage than the patients who received low dose. The efficacy and safety of this vaccine is being further investigated in the ongoing Phase III trial where the primary endpoint is survival.

Advax™ is a novel polysaccharide vaccine adjuvant that is being developed by Vaxine Pty Ltd in Adelaide, Australia across a range of vaccine indications including cancer. Promising enhancement of cancer vaccine efficacy has been obtained with Advax™ adjuvant in pre-clinical studies and it is hoped that human cancer vaccine trials including the adjuvant will commence shortly.

**Immunoglobulin E Anti-cancer Therapy**

Recent interest has focused on the potential role of Immunoglobulin E (IgE) as a mediator of anti-cancer effects. As IgE comprises only 0.02% of the total antibody in humans, specific anti-tumour IgE faces less competition for cell surface receptors than other immunoglobulin subtypes. Moreover, IgE is able to induce antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis via high- and low-affinity receptors, FceRI and CD23. As the affinity of IgE for FceRI is two to five orders of magnitude higher than that of IgG, IgE should potentially be more potent in tumour destruction. Thus far it has been difficult to specifically generate IgE antibodies in response to vaccination, which more typically induces IgG antibodies. Recently an animal model has been developed in which IgE was induced by epitope-specific vaccination against the tumour antigen HER-2, using an oral immunization regimen, fed under concomitant gastric acid suppression. However, considerable further research would be required before this model could be translated to human trials.

**Conclusions**

New therapeutic strategies are required in the treatment of cancer. Vaccines and other immunotherapies offer an attractive alternative to current treatments such as chemotherapy. After failures of many cancer vaccine trials and widespread loss of faith in the field, signs of hope are emerging with recent commercialization of Provenge, the first FDA-approved human cancer vaccine. This has helped to re-invigorate the cancer vaccine field, with renewed research into identification of additional tumour antigens to be used as vaccine targets, investigation of new vaccine adjuvants to better enhance the immunogenicity and potency of cancer vaccines, and exploration of new vaccine delivery techniques such as DNA vaccines, which may be able to better stimulate an anti-tumour cytotoxic T-cell response. Hence, while it has been a long road travelled, cancer vaccines are currently undergoing a major revival, and it is hoped that this will result in additional regulatory approvals in coming years. Whilst Provenge has not been a major commercial success, this largely reflects the fact it is a complex dendritic cell (DC) vaccine. Without a doubt, a more traditional protein-based vaccine that doesn't require the use of the patient's own white blood cells is likely to be much more attractive to patients and doctors and thereby more commercially successful.

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