

# Lung cancer vaccines: current status and future prospects

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**Abstract:** Designing a cancer treatment that very specifically targets and kills tumor cells with little to no side effects is the “holy grail” of oncology. Cancer vaccines have this potential. Vaccines utilize the immune system to specifically target and eliminate tumor cells. Historically, vaccination approaches against lung cancer have been disappointing. However, over the past decade, a greater understanding of the immune system and of the antigens expressed by tumors, coupled with advances in immunoadjuvants and improved delivery systems, has led to advances in the use of immunotherapy including vaccines to target lung cancer. Proof of principle phase I/II clinical trials targeting the MAGE-A3 and MUC1 tumor antigens, as well as cell-based vaccines such as belagenpumatucel-L have suggested improved survival, leading to larger scale phase III clinical trials. This review will discuss cancer vaccines in relation to lung cancer and present clinical data supporting their use.

**Keywords:** Lung cancer; cancer vaccines; immunotherapy; clinical trials



Submitted Oct 07, 2013. Accepted for publication Dec 03, 2013.

doi: 10.3978/j.issn.2218-6751.2013.12.01

Scan to your mobile device or view this article at: <http://www.tlcr.org/article/view/1850/2726>

## History of cancer vaccines

The idea of using a patient’s immune system to attack their cancer is not a new concept. In 1891, William Coley began what is regarded as the first American trial of immunotherapy to treat cancer (1). Coley based his study on observations of a number of patients that developed erysipelas and other bacterial infections and subsequently experienced spontaneous tumor regressions. Coley injected live *Streptococcus pyogenes* into patients’ tumors with the idea that the body would fight off the infection and as “collateral damage” the tumor would also be destroyed. The first patient that Coley treated developed high fevers, chills and intense headache, consistent with bacterial sepsis. The patient also experienced hemorrhagic necrosis of their tumor leading to tumor shrinkage and a remission. The idea of using live bacteria in a pre-antibiotic era was not ideal and subsequently a number of patients died from sepsis after receiving live bacterial treatments. In response, Coley modified his “vaccination” to use cell-free filtrates of mixed bacterial cultures of *Streptococcus* and *Serratia marcescens*

(Coley’s toxins) with some reports of responses. The advent of chemotherapy and radiation therapy largely relegated Coley’s work into the history books until the 1970s when *Bacillus Calmette-Guerin* (BCG) was successfully studied as a treatment for early stage bladder cancer. BCG was approved by the Food and Drug Administration (FDA) in 1990 as a first-line treatment for superficial bladder cancer and remains the treatment of choice for this disease. While BCG immunotherapy has shown efficacy in bladder cancer, it has been largely ineffective in other tumors such as lung cancer (2).

Today most cancer vaccine research is focused on specifically targeting known or unknown tumor-associated antigens (TAA). The first therapeutic cancer vaccine to be approved by the U.S. FDA is sipuleucel-T (Provenge®). Sipuleucel-T was approved in 2010 to treat asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC). It consists of antigen presenting cells (APCs) derived from patient’s peripheral blood mononuclear cells obtained by leukapheresis, and cultured with a recombinant fusion protein consisting of human

prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF) (3). Up to 95% of prostate cancer overexpresses PAP. PAP is a non-essential protein and its expression is largely limited to the prostate making it a near ideal target antigen (4). By culturing the APCs with the PAP-GM-CSF fusion protein, they are matured. The mature PAP-specific APCs are re-infused into the patient and can generate PAP specific immunity and thereby tumor specific immune responses. Approval for sipuleucel-T was based on two phase III clinical trials. The first study enrolled 127 patients with asymptomatic metastatic CRPC were randomly assigned to receive sipuleucel-T (n=82) or placebo (n=45) (5). The trial showed that there was no statistical difference in time to disease progression, the primary endpoint of the study; however, when retrospectively analyzed for median survival, there was a significant increase in patient survival with the median survival of patients receiving sipuleucel-T at 25.9 months compared with 21.4 months for patients receiving placebo. Based on this finding, a second study, the IMPACT trial, was initiated. Patients were randomized in a 2:1 ratio to receive sipuleucel-T (n=341), or control (n=171). The primary end point of this study was overall survival. Patients receiving sipuleucel-T had a median overall survival of 25.8 months compared with 21.7 months for patients receiving the placebo. This 4.1 months extension in median survival was significant (6).

To date, sipuleucel-T is the only vaccine approved to treat established tumors. A number of other vaccines are being tested in late stage clinical trials. This review will focus on the major vaccine clinical trials designed to treat lung cancer.

### Lung cancer vaccines

Until recently, lung cancer has proven difficult to treat with immunotherapy strategies such as vaccines. The normal lung environment is constantly exposed to foreign antigens, including inanimate dust, viruses, bacteria and fungi. Immune cells within the lung must mount an appropriate response to pathogenic threats while inhibiting aberrant immune responses. Imbalances in immune activation and immune suppression can lead to autoimmune diseases such as asthma or interstitial lung disease. Lung cancers may tip the immune activation-immune suppression balance to favor immune suppression attenuating host responses against the tumor, and allowing tumor progression. Evidence for this has been reported in non-small cell lung

cancer (NSCLC) that has been shown to be infiltrated with increased numbers of immunosuppressive CD4+CD25+ T regulatory cells (7). These cells have also been shown to express transforming growth factor- $\beta$  (TGF- $\beta$ ) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) that can inhibit immune responses leading to immune tolerance to tumor associated antigens (8). IL-10 has also been shown to be expressed by some NSCLCs resulting in the inhibition of T-cell proliferation and the secretion of pro-inflammatory cytokines leading to immune tolerance (9). Generating vaccines to target lung cancer requires shifting the immune activation-immune suppression balance in favor of immune-activation.

### Protein and peptide vaccines

Over 70 proteins have been identified as tumor associated antigens (TAAs). These include viral antigens such as human papilloma virus E6 and E7 expressed in cervical cancer and head and neck cancers; cancer-testis antigens such as MAGE-A3 whose expression is limited to male germ line cells and cancerous cells including lung cancer; and over expressed antigens such as MUC-1 which is minimally expressed in epithelial cells, but over expressed in cancer. Targeting these using whole protein or peptide vaccines provides a rational approach to preferentially kill tumor cells.

#### *MAGE-A3 vaccines*

Melanoma-associated antigen-3 (MAGE-A3) is an antigen that is expressed primarily on tumor cells. It is not expressed on normal cells except in the male germ cells that also lack MHC class I molecules that present antigen to the immune system. The lack of MHC-I limits presentation of MAGE-A3 by the germ cells thus limiting their targeting by the immune system (10). MAGE-A3 is expressed in about 35% of NSCLCs, with an increasing expression from approximately 30% of stage I patients to 50% of stage II patients (11). Greater expression of MAGE-A3 is thought to be related to more advanced disease and a poorer prognosis (12).

The efficacy of MAGE-A3 as a vaccine target in NSCLC was evaluated in a multicenter, double-blinded phase II clinical trial. In this trial, 182 stage I and II patients with completely resected tumors were assigned to receive postoperative recombinant MAGE-A3 protein plus adjuvant or placebo in a 2:1 ratio. Patients were vaccinated every three weeks for a total of five cycles followed by eight

vaccinations given every three months. No serious side effects were observed during treatment. After a median follow up of 28 months, hazard ratios of disease-free survival and overall survival were 0.73 (95% CI: 0.45-1.16) and 0.66 (95% CI: 0.36-1.20), respectively. There was a 27% improvement in time to progression and disease-free survival in patients receiving the vaccine. This was not statistically significant. Despite this, the results were promising enough to justify a phase III trial (13).

The phase III MAGRIT (MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy) trial started enrolling curatively resected patients whose lung cancers were MAGE-A3-positive in 2007. The estimated enrollment for the study are 2,270 stage IB, II and IIIA NSCLC patients assigned to either the MAGE-A3 group, or a placebo group. The primary endpoint of the MAGRIT trial is disease-free survival with secondary endpoints of overall survival, yearly disease-free survival from 2-5 years, lung cancer-specific survival, disease-free specific survival, and adverse events (14). While the MAGRIT trial is not expected to release results until 2014, the initial results of a similar phase III trial targeting MAGE-A3 in melanoma (DERMA Trial) has been released (<http://www.gsk.com/media/press-releases/2013/the-investigational-mage-a3-antigen-specific-cancer-immunotherap.html>). This trial showed that the MAGE-A3 vaccine did not significantly extend disease-free survival in patients with melanoma expressing the MAGE-A3 antigen when compared to placebo, and therefore failed to meet its primary end-point. While the data for overall survival and disease-free survival in the gene signature-positive subpopulation is yet to be released, the results of the DERMA trial are disappointing and lowered the expectations of positive results from the MAGRIT trial.

### *L-BLP25 (Stimuvax<sup>®</sup>, Tecemotide)*

Mucin 1 (MUC1) is a highly glycosylated transmembrane protein that is found on the apical surface of most epithelial cells of the respiratory, genitourinary and digestive system (15). In many cancers it is overexpressed and abnormally glycosylated making tumor-associated MUC1 immunologically distinct from the MUC1 found on normal cells (16). High levels of MUC 1 are believed to enhance immunosuppression and predict a poor prognosis in patients with adenocarcinomas (17). MUC1 is thought to be involved in the formation and migration of tumor cells and can demonstrate increased immunogenicity, making it

an attractive target for immunotherapy.

L-BLP25 (Stimuvax<sup>®</sup>) is a liposome-based vaccine that targets MUC1. The vaccine is composed of an immunogenic peptide of MUC1 (BLP25 lipopeptide), immunoadjuvant monophosphoryl lipid A, and three lipids (cholesterol, dimyristoyl phosphatidylglycerol, and dipalmitoyl phosphatidylcholine). A randomized phase IIb study of L-BLP25 in stage IIIB and IV NSCLC was conducted looking at survival and toxicity in patients (18). Of the 171 patients recruited to the study, 88 were assigned to L-BLP25 plus best supportive care (BSC) and 83 received BSC alone.

The study showed that the median survival time of the patients receiving the immunotherapy was 4.4 months longer than that of patients that received BSC alone. In an updated survival analysis of these patients, median survival time was 17.2 months in patients receiving L-BLP25 plus BSC when compared to 13.0 months in patients receiving BSC alone (4.2 months difference) while the 3-year survival rate was 31% compared to 17% respectively (19).

Based on these results, a randomized phase III trial of patients with unresectable stage III NSCLC who did not progress after primary chemotherapy and radiation was initiated to examine L-BLP25 compared to placebo (START trial). The 1,513 enrolled patients were randomized in a 2:1 double-blinded schema to L-BLP25 or placebo. Patients treated with L-BLP25 received low dose cyclophosphamide three days before treatment, to reduce the activity of suppressor T-cells. L-BLP25 was given weekly for eight weeks with maintenance vaccination therapy following this at six weeks intervals. In patients treated with L-BLP25 the median overall survival was 25.6 months compared to 22.3 months with placebo (adjusted HR 0.88, 95% CI: 0.75-1.03, P=0.123). This overall survival was not significantly different, therefore the START trial failed to meet its primary end-point. Interestingly, when looking at those patients treated with L-BLP25 and concurrent chemotherapy and radiation (n=538) there was a significant survival advantage over placebo (n=268), with a median overall survival of 30.8 months (L-BLP25) compared to 20.6 months (placebo; HR 0.78, 95% CI: 0.64-0.95, P=0.016) (20,21). Based on this finding, a new phase III clinical trial has been announced (START2 trial) with a primary end-point of overall survival in patients undergoing concurrent chemo-radiation therapy treated with L-BLP25 or control.

A similar phase III study to START looking at L-BLP25 compared to placebo in the Asian population (INSPIRE) is

also currently recruiting patients with an estimated accrual of 420 individuals (22).

### Cell-based vaccines

Although a number of TAAs have been identified and can be targeted by protein or peptide vaccines, there are as of yet many more unidentified TAA expressed by tumors. To solve this problem, whole tumor vaccines have been developed where “killed” or inactivated tumor cells are used as the vaccine platform. The vaccine tumor cells express many of the same TAAs that are expressed on the patient’s cancer so in theory an immune response to the cancer can be generated. These vaccine tumor cells can be harvested from the patient’s own tumor (autologous) or from established cancer cell lines of similar tumor types (allogeneic) and are often genetically modified to make them more immunogenic.

#### GVAX<sup>®</sup>

GVAX consists of irradiated autologous or allogeneic tumor cells genetically modified to secrete recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF). GVAX has been shown to induce the infiltration of antigen presenting dendritic cells into the vaccine site, and stimulate CD8+ and CD4+ T-cell responses, as well as antibody responses (23). The GVAX platform has been studied in a number of cancer types including melanoma, renal cell carcinoma, prostate cancer and NSCLC. Two phase III randomized, controlled trials of GVAX in prostate cancer (VITAL-1 and VITAL-2) were conducted to evaluate the benefits of GVAX-prostate versus standard chemotherapy (docetaxel and prednisone). In VITAL-1, GVAX-prostate alone was compared to chemotherapy whereas in VITAL-2, GVAX plus chemotherapy was compared to chemotherapy alone. Both trials were terminated early due to a lack of efficacy (24,25). Additionally, in the VITAL-2 study an increase in patient deaths was also noted in the GVAX treated arm.

Despite these disappointing results for GVAX-prostate, early trials of GVAX in NSCLC have shown some promise. In a Phase I trial for patients with stage IIB-IV NSCLC, a successful autologous vaccine was created for 34 patients (97%) (26). The vaccine was administered weekly for three weeks and then biweekly until the patient was removed from the study or there was no vaccine supply left. The most common adverse event noted was local skin reaction

at the vaccination site. Five patients showed stable disease; one patient had a mixed response and two patients that had undergone prior surgical resection showed no evidence of disease for over 42 months.

Following this trial, a phase I/II study using GVAX-NSCLC was conducted (27). Here, 83 patients, 20 with early stage (I/II) and 63 with late stage (III/IV) were enrolled in the study. Vaccinations were given to ten patients with early stage and 33 patients with late stage NSCLC. Patients were administered  $5 \times 10^6$  to  $100 \times 10^6$  vaccine cells per dose for 3-6 biweekly vaccinations, followed by monthly treatment for six months. GVAX-NSCLC did not show dose-limiting toxicity with local reactions at the vaccination site being the most common. Three of the late stage patients with extensive disease had durable, complete regression of tumor, two of which has had complete regression for over five years. Despite some promising results in NSCLC, the negative VITAL trials for prostate cancer have limited the enthusiasm for conducting phase III trials with the GVAX platform at this time.

#### *Belagenpumatucel-L (Lucanix<sup>®</sup>)*

Belagenpumatucel-L is a genetically modified allogeneic tumor cell vaccine that inhibits transforming growth factor  $\beta 2$  (TGF- $\beta 2$ ). It was developed from five established allogeneic NSCLC cell lines that are transfected to express an antisense TGF- $\beta 2$  sequence to inhibit the expression of TGF- $\beta 2$ . TGF- $\beta 2$  is an isoform in the TGF- $\beta$  family and is found to be immunosuppressive, exhibiting antagonistic effects on natural killer cells, activated killer cells and dendritic cells (28). The expression of TGF- $\beta 2$  has been correlated to poor prognosis in NSCLC.

A randomized phase II clinical trial on 75 NSCLC patients (stages II-IV) has been completed. Patients were assigned into one of three doses ( $1.25 \times 10^7$ ,  $2.5 \times 10^7$  or  $5 \times 10^7$  cells/injection) and were treated monthly or once every two months. Only minor adverse events were noted with only one grade 3 toxicity attributed to the vaccine. The results demonstrated that there was a partial response rate of 15% in the advanced stage patients. The estimated probability of surviving one or two years was 39% and 20% respectively for patients receiving the low dose of the vaccine ( $1.25 \times 10^7$  cells/injection). This compared to 68% and 52% for the higher doses ( $2.5 \times 10^7$ - $5 \times 10^7$  cells/injection). The estimated median survival time for patients in the low dose category was 252 days compared to 581 days for patients in the higher doses (29).

Based on these results a randomized phase III clinical trial was initiated to examine the overall survival benefits to patients with stages T3N2-IIIa, IIIB, and IV who did not progress after frontline chemotherapy and were treated with belagenpumatucel-L or placebo (STOP trial). The trial enrolled 532 patients, with patients receiving treatments between 4 and 17.4 weeks from the end of frontline chemotherapy. Patients were further randomized into tumor histology with 57% adenocarcinoma, 27% squamous, and 6% large cell carcinoma. Patients were administered belagenpumatucel-L or placebo over 18 months and two quarterly intradermal injections until disease progression or withdrawal from the trial. The STOP trial did not meet its primary end point with median overall survival of patients treated with belagenpumatucel-L at 20.3 months compared to 17.8 months for the placebo (HR 0.94;  $P=0.594$ ). Patients who were treated within 12 weeks of chemotherapy completion showed improvement in overall survival with median overall survival of 20.7 months with belagenpumatucel-L compared to 13.4 months with placebo (HR 0.75;  $P=0.083$ ). Patients who had been pretreated with radiation had a median overall survival of 40.1 months (Belagenpumatucel-L) compared to 10.3 months (placebo), (HR 0.45;  $P=0.014$ ). Interestingly, patients with stage IIIB/IV non-adenocarcinoma randomized within 12 weeks of the completion of chemotherapy ( $n=99$ ) had median overall survival of 19.9 months (belagenpumatucel-L) compared to 12.3 months (placebo), (HR 0.55;  $P=0.036$ ) (30). While the results for the STOP trial did not meet the primary endpoint the marked improvement in survival obtained in identified specific subgroups of patients is an encouraging step for lung cancer vaccines and further trials are planned.

### Adoptive T-cell therapy

Adoptive T-cell therapy (ATcT) is a passive vaccine strategy that involves the transfusion of T-lymphocytes into a patient to attack tumor cells. There are two main approaches for generating T-cells that will target tumor cells. The first is to use T-cells with endogenous T-cell receptors (TcRs) that can recognize tumor. This is usually achieved by isolating tumor infiltrating lymphocytes (TILs) from the patient's tumors and expanding them *ex vivo*. The TILs have been shown to have specificity for the tumor and can be used to target and kill tumors even in heavily pretreated patients (31).

The second approach involves the genetic manipulation of the T-cell so that it expresses a TcR or antibody fragment that recognizes a tumor-derived antigen. The genetically

modified T-cell can then target and destroy tumors expressing that antigen (32).

A TcT has shown promise in phase I and II clinical trials for the treatment of melanoma. In a recent phase II study, Rosenberg and colleagues reported the results of 93 patients who had progressed on standard treatment and were treated with TILs plus IL-2. An objective response was seen in 52/93 (56%) of patients treated with TILs. Twenty patients (22%) had complete regression of their disease, with 19 having ongoing complete responses in excess of three years (31). In another recent study using T-cells genetically modified to express the NY-ESO-1 tumor antigen-specific TcR, Robbins *et al.* reported a measurable response rate in synovial cell sarcoma patients of 66% (4/6) and in melanoma patients of 45% (5/11), with two melanoma patients being ongoing complete responders (33). This trial also reported that none of the patients who received NY-ESO-1-specific T-cells experienced off-target toxicity.

ATcT has also shown efficacy in other malignancies including lung cancer. A trial comparing therapy with TILs and IL-2 versus standard therapy was conducted in 113 patients with surgically resected stages II, IIIa and IIIB NSCLC. Patients were divided based on stage of disease and randomized into the adoptive immunotherapy group and the standard chemoradiotherapy or control group. Both arms had surgical resection of tumors and received the same radiotherapy regimen. The control arm received vinblastine and cisplatin while the adoptive immunotherapy group received TILs 6-8 weeks after surgery and escalating doses of recombinant IL-2 (rIL-2) for two weeks from the day of TIL infusion, then reduced doses for two weeks followed by 2-3 months (34). The results showed that ATcT with TILs resulted in significantly enhanced 3-year survival compared to the control group. ATcT was significantly advantageous to patients with stage IIIB (T4) NSCLC ( $P<0.01$ ) as well as in patients with local relapse of stage III disease but was of no benefit to patients with stage II NSCLC. This study showed that adoptive therapy may be beneficial to some NSCLC patients in the adjuvant setting. Further studies including greater numbers of lung cancer patients are necessary to elucidate whether TIL therapy is beneficial.

### Conclusions and future prospects

With the overall 5-year survival rate of lung cancer being just 15-16% there is a great need for new treatments. Using the immune system to target and destroy lung cancer would seem ideal. However, to date, the only

immunotherapy treatment to be approved for lung cancer is the antivascular endothelial growth factor monoclonal antibody, bevacizumab. Early clinical trials using vaccines to target lung cancer have had mixed results. Possible reasons for this are:

(I) It has been difficult to identify and target antigens that are expressed predominantly or exclusively by the tumor. Many currently identified TAA have been shown to be weakly immunogenic limiting their effectiveness. Identifying novel TAA or targeting multiple antigens may result in more effective treatments.

(II) An inability to effectively break immune tolerance to the tumor associated antigens: the lung is a largely tolerizing environment. Combining immune stimulating agents (e.g., cytokines or vaccines) with immune checkpoint blockade (e.g., ipilimumab or anti-PD-1 monoclonal antibody) to inhibit tolerance may be required to get a better immune response in the lung.

(III) Targeting the wrong lung cancer patients. Most clinical trials of new immunotherapy agents, such as cancer vaccines are tested in patients with advanced with large tumor burdens. Instead cancer vaccines may be more effective and appropriate to use in limited disease or after curative intent resection.

Despite limitations, lung cancer vaccines remain a promising and active area of investigation. Targeting of specific subpopulations in the ongoing phase III trials of L-BLP25, MAGE-A3 and the belagenpumatucel-L vaccines have highlighted suggest benefit of lung cancer vaccines. They have also shown the importance of combining vaccines with chemotherapy and radiation in a multimodality approach targeting lung cancer.

## Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

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**Cite this article as:** Ramlogan-Steel CA, Steel JC, Morris JC. Lung cancer vaccines: current status and future prospects. *Transl Lung Cancer Res* 2014;3(1):46-52. doi: 10.3978/j.issn.2218-6751.2013.12.01