Oncologic, Endocrine & Metabolic

Present and future of lung cancer vaccines

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New approaches are needed to improve the current treatment of lung cancer. Inducing an immune response against lung tumour cells with vaccines represents an attractive therapy. However, lung tumours had not been considered good targets for vaccine therapy and, therefore, immune approaches have not been studied extensively in this setting. Current experimental strategies for antitumour vaccines include the generation of active immune responses against specific tumour antigens. Understanding the mechanisms of antitumour immunity and identifying relevant tumour-specific antigens will probably improve therapeutic strategies and provide avenues for the future of lung cancer therapy. There have been a number of preclinical immunotherapy trials suggesting activity, and a smaller number of human clinical trials using various vaccines in lung cancer. Initial data from these trials have shown preliminary evidence of induction of immune responses and suggest clinical activity. This paper reviews some of the most important developments in vaccines for lung cancer.

Keywords: B7.1, BEC, GVAX, immunotherapy, MUC1, non-small-cell lung cancer, small-cell lung cancer, vaccine


1. Background

A major issue in the attempt to develop immunotherapy for lung cancer is the ability to generate an adequate immune response in the host with relative selectivity for lung cancer cells. Immunotherapy may involve differing approaches, including the use of monoclonal antibodies (passive immunotherapy), cytokines such as IFN-α, IL-2 or bacterial adjuvants (active nonspecific immunotherapy) and vaccination (active specific immunotherapy). Historically, non-small-cell lung cancer (NSCLC) tumours have not been perceived as good targets for active specific immunotherapy or vaccination, because in general, NSCLC tumours have been considered to be nonimmunogenic. We also now know that NSCLC tumours contain CD4+CD25+ regulatory cells (T-regulatory cells [T-regs]), which are suppressive for cytotoxic T lymphocyte (CTL) generation [1]. Moreover, suitable target antigens in lung cancer have not yet been identified. For these and other reasons vaccines targeting lung cancer have not been studied extensively. Therefore, several clinical trials for NSCLC focused primarily on the use of autologous and/or allogeneic whole-tumour cell-derived vaccines, rather than on specific antigens or peptides [2]. Recent advances in immunology and molecular biology may allow identification of new antigens that may provide new targets.

Antigen presentation in draining lymph nodes is the first step in triggering an immune response. Once CTL clonal expansion and differentiation occur, CTLs are released into the bloodstream and migrate to the tumour tissue by a complex system of chemotactic and adhesion receptors. The initial growth of a tumour has been
linked to the failure of immune surveillance of the host. In order for a malignant clone to proliferate and propagate, it has to evade the immune system. Several mechanisms may lead to immune evasion (Figure 1). The first mechanism is the failure to prime the immune system. Tumours such as NSCLC ('poorly' immunogenic tumours) escape recognition by down-regulation of MHC molecules and secretion of NKG2D ligands (cell surface receptor expressed on natural killer [NK] cells) [3]. Several factors have been associated with the lack of adequate priming, including immune suppressive factors secreted by tumours such as: TGF-β, IL-10, phosphatidyl-serine, prostaglandins and soluble NKG2D-ligand, which can lead to induction of anergy or tolerance and increased activity of T-regs [3-6].

A second mechanism of tumour immune evasion is the blockade of the effector phase and lack of efficacy of effector cells against tumour cells. Numerous tumours elicit an immune response, as evidenced by the accumulation of tumour-infiltrating lymphocytes (TILs). Although TILs have tumour specificity and the correct phenotype of CTL, many cancer cells may develop defence mechanisms that can neutralise effector cell activity and thereby evade immune destruction. Priming and proliferation of CTLs occur in draining lymph nodes and then CTLs leave the node and enter the bloodstream. Within the tumour vasculature, CTLs must extravasate, enter the tumour tissue (so-called TILs) and locally exert antitumour effector function. Furthermore, pre-clinical and clinical data suggest that T-reg (a subset of T lymphocytes expressing CD4+CD25+) can also play a major role in downregulating immune responses to tumours, including lung cancer, by limiting the expansion of effector clones [7,8]. It may be possible to selectively deplete these cells with the use of anti-CD25-directed toxins (denileukin diftitox) or antibodies, or inhibit their activity by other means such as engagement of glucocorticoid-induced TNF receptor (GITR) by GITR ligand, and thus improve antitumour response [9].

2. Medical need

Lung cancer is the leading cause of cancer deaths in the US, with 163,510 deaths estimated in 2005, including 15,000 – 20,000 patients that are considered never smokers [10,101]. Only a small group of patients are able to have surgery with curative intent and even in that scenario relapse is a frequent event. Lung cancer carries a 5-year survival of only 10 – 15% for all stages [11,12]. Large randomised clinical trials using the best chemotherapy regimens available (third-generation platinum-based regimens with paclitaxel, docetaxel, gemcitabine or vinorelbine) have reported similar, but limited, activity with response rates that has varied in the range of 15 – 22%, with 1-year survival rates of 31 – 36%. Median survivals of only 10 – 11 months are seen in patients with metastatic disease, who represent the majority of NSCLC patients [13-15]. Chemotherapy is given in the adjuvant setting with modest effect on survival and in the metastatic setting with palliative intent.

EGFR inhibitors are now used in the treatment of NSCLC. Erlotinib (a tyrosine kinase inhibitor) is now approved for use as monotherapy in treatment-refractory, advanced NSCLC. The randomised Phase III trial called BR21, which investigated erlotinib as second- or third-line therapy in metastatic NSCLC, demonstrated a significant overall survival benefit from erlotinib monotherapy [16]. However, this benefit is restricted to a minority of patients and most of the patients who respond to therapy eventually will progress.

It is clear that new therapeutic options are needed to improve the current management. Immunotherapy for lung
cancer may provide a new therapeutic option to improve outcomes in NSCLC.

3. Existing treatment

Lung cancers are usually divided in two groups according to the pathology at diagnosis: small-cell lung cancer (SCLC) and NSCLC, which includes most tumours (adenocarcinomas, squamous-cell carcinomas, large-cell carcinomas, etc.). There are also differences in the choice of chemotherapeutic agents for SCLC or NSCLC. There are no vaccines approved for any indication in the therapy for NSCLC. The mainstay of treatment for most patients (stages IIIB/IV) is still palliative chemotherapy. Large meta-analyses have demonstrated a significant survival advantage in favour of chemotherapy versus best supportive care [17,18]. Furthermore, three randomised Phase III trials, including 1200 patients, have established that response rates and time to progression are improved with combination chemotherapy over single-agent therapy [19-21]. Large clinical trials comparing various third-generation, platinum-based chemotherapy, radiation and BCG immunotherapy [35], 5 of a cohort of 58 SCLC patients treated during the 1970s with disease following curative chemotherapy and radiation. Of a because it was feasible to treat patients with minimal residual disease [33,34]. At that time, SCLC was commonly investigated on nonspecific immune stimulants including thymosin, Bacille Calmette-Guerin (BCG) vaccination and other immune adjuvants [33,34]. At that time, SCLC was commonly investigated because it was feasible to treat patients with minimal residual disease following curative chemotherapy and radiation. Of a cohort of 58 SCLC patients treated during the 1970s with chemotherapy, radiation and BCG immunotherapy [35], 5 of 19 patients (26%) with limited stage disease were long-term survivors. Two larger series of patients with lung cancer treated with BCG revealed improvements in survival compared with historical controls, and these studies also suggested a modest survival benefit for patients undergoing intrapleural injection for patients in the setting of pleural effusions [36,37]. Patients with adenocarcinomas were reported to respond better than those with squamous-cell carcinomas [38]. Excitement about nonspecific agents was tempered; however, because a randomised study of BCG as adjuvant therapy for SCLC demonstrated no impact on overall survival [39]. In addition, a study of preoperative intratumoural injection of BCG found no impact on disease-free survival or overall survival [40]. However, both of these randomised trials were underpowered to detect small differences. So far, BCG has been employed as an adjuvant in the setting of autologous tumour or antigen-specific vaccine trials [41], but has not been accepted as a useful modality for lung cancer therapy.

The T-cell growth factor thymosin, another nonspecific immune stimulant, was found to have minimal activity in combination with chemotherapy [33]. Similarly, early studies using the bacterium Corynebacterium parvum (as a systemic antitumour agent for NSCLC) demonstrated dose-related tumour responses, but no effect on overall survival [34].

During the 1990s, nonspecific immunotherapy was attempted using IL-2, other cytokines or inflammatory mediators. Schiller and colleagues reported a series of 15 patients with advanced lung cancer treated with IL-2 and TNF-α. Cardiopulmonary toxicity was significant and there were no significant tumour responses. Similarly, a combination of IL-2 and IFN-α demonstrated little or no benefit [43]. In another study, the combined therapy of IL-2 and melatonin demonstrated clinical benefit (20% partial response, 50% stable disease) in a pilot study of 20 patients [44].

Monoclonal antibodies are now widely employed for therapy of lymphoma (e.g., rituximab, alemtuzumab), breast cancer (e.g., trastuzumab) and colon cancer (e.g., bevacizumab, cetuximab). Several of these antibodies have been introduced in the treatment of lung cancer with a series of preclinical and clinical trials. In preclinical studies, an antibody targeting the ganglioside fucosyl GM1 was shown to inhibit growth of metastatic lung cancer via antibody dependent cell-mediated cytotoxicity [45]. In humans, trastuzumab (anti-HER-2/neu antibody) was evaluated in combination with chemotherapy for advanced NSCLC [46]. In this study, none of 13 HER-2/neu-positive patients responded to targeted therapy. Recently, clinical trials have shown that combination of conventional chemotherapy (platinum-based doublet) and the antiangiogenic antibody bevacizumab improved progression-free survival, 1-year survival and overall survival in patients with metastatic NSCLC [47-49].

Antigen-specific radioimmunotherapy has been attempted for SCLC by using bispecific monoclonal antibodies. This was felt to be a promising treatment strategy because SCLC is highly radiosensitive. In one study, anticarcinoembryonic antigen (CEA) antibody was attached to a radionuclide-binding antibody. Of 12 patients, 3 responded to this treatment [50]. This targeting strategy for delivery of radionuclides has not been fully explored and offers considerable promise. However,
the absence of reliable shared membrane target antigens with selectivity for N SCLC may limit the use of this approach.

Another alternative is the targeting of the antigenic determinants on N SCLC cells through vaccination strategies to evoke an endogenous antibody and/or cytolytic immune response. Although lung cancer is not known to be immunogenic, once a response is primed lung cancer may provide an accessible target for properly primed immune effector cells [51].

In a large immunotherapy trial conducted for lung cancer with the BEC2–BCG vaccine, BEC2 was combined with BCG in a pilot study that enrolled 15 patients, including those with limited and extensive SCLC, after they had been treated with standard chemotherapy and had attained maximal response [52]. Patients received a series of five intradermal immunisations consisting of BEC2 plus BCG over a 10-week period. All patients developed anti-BEC2 antibodies and five patients developed anti-GD3 antibodies, including several of those with the longest relapse-free survival. The median relapse-free survival for patients with extensive disease was 11 months and was not reached for patients with limited disease (>47 months) at the time of publication, with only one out of seven patients having a recurrence after a median follow-up of 47 months.

Immunotherapy shown to be safe and capable of inducing an immune response against the GD3 ganglioside in SCLC after standard chemotherapy was given using BEC2 plus BCG. The survival and relapse-free survival in that cohort of patients was substantially better than those observed in historical controls, leading to the development of a large international Phase III trial. The results the SILVA study (Survival in an International Phase III Prospective Randomized Limited Disease Small Cell Lung Cancer Vaccination Study with Adjuvant BEC2 and BCG) were presented at the 2004 American Society of Clinical Oncology (ASCO) meeting [53]. In that study, a total of 515 patients diagnosed with limited disease SCLC who responded to four to six cycles of chemotherapy and thoracic radiation therapy were randomised to observation (n = 258) or vaccination with BEC2 (n = 257). As of June 2004, when the results were released, 71% of the patients had progressed and 72% had died. No differences in progression-free and overall survival between observation and vaccination arms were observed. The study concluded that BEC2/BCG did not confer survival advantage after a major response from concurrent chemotherapy and radiation.

We can see how historically we have evolved from passive immunological strategies and nonspecific immunotherapy to the development and identification of tumour-associated antigens that have enabled the development of vaccines that prime potent, antigen-specific immune responses. Now that tumour antigens such as the ganglioside fucosyl GM 1 have been identified, targeted active immunotherapy strategies have become feasible. In the last year the benefit of incorporating cytokines into antitumour vaccines has been well established. The cytokine GM-CSF, a significant mediator of proliferation, maturation and migration of dendritic cells, has been shown to enhance the generation of potent, durable antitumour immunity (reviewed in Section 5 in clinical trials in which it has been involved). Another promising strategy is the incorporation of costimulatory molecules into tumour vaccines, an example of which is the vaccine B7.1; tumour cells transfected with B7.1 and human leukocyte antigen (HLA) molecules have been shown to stimulate an immune response by direct antigen presentation and activation of T cells without intermediary cells.

5. Current clinical trials with specific immunotherapy against lung cancer

Most clinical trials in immune therapy of lung cancer are in early development. A short summary of several of the more promising trials at this point is presented in Table 1, and the trials are discussed according to the type of lung tumour: N SCLC or SCLC.

5.1 Clinical trials for non-small-cell lung cancer

5.1.1 GVAX–GM-CSF-transduced autologous tumour cells

In the initial GVAX® (Cell Genesys) trial, resected N SCLC metastases from 35 patients were processed to single-cell suspension, transduced with a replication-defective adenoviral vector encoding the human GM-CSF gene, irradiated and cryopreserved. In the first GVAX study, the vaccine was produced and given to 34 patients [54]. Most of the patients had adenocarcinomas (19 tumours), the remaining having bronchioalveolar carcinomas (BAC), squamous-cell carcinomas, large-cell carcinomas or mixed histologies. Patients received intradermal and subcutaneous vaccinations weekly for 2 weeks followed by biweekly vaccinations until the supply was exhausted. Toxicities were restricted to grade 1 and 2 local skin reactions. Nine patients progressed rapidly and were withdrawn from the study. GVAX vaccinations induced infiltrates at the injection site of dendritic cells, macrophages, granulocytes and lymphocytes in 18 out of 25 patients. Metastatic lesions regressed after vaccination revealed tumour necrosis and TILs in three out of six patients. Five patients treated at dose level 2 had stable disease at 33, 19, 12, 10 and 3 months, respectively.

Nemunaitis and colleagues reported a Phase I/II multi-centre trial treating patients using irradiated autologous tumour cells transduced to secrete GM-CSF [55,56] in order to elicit antitumour activity in patients with early and advanced-stage N SCLC. Tumours were harvested from 83 patients, but only 43 patients (10 with early stages I/II and 33 advanced stages III/IV) were vaccinated. The most common toxicity was a local injection-site reaction (93%). Of 33 advanced-stage patients (refractory to standard therapy), 3 (2 of them with BAC) achieved a complete response. The duration of the complete responses was > 6 months. Longer median survival (17 months) was observed in those patients receiving vaccines secreting 'higher' levels of GM-CSF than in patients receiving vaccines secreting less GM-CSF (median survival was
7 months). However, measurements of immunological responses were not associated with clinical response or survival. Southwest Oncology Group (SWOG) 0310 protocol was a study in which GVAX was given to selected stage IIIB and IV BAC. The study required tumour harvesting via thoracoscopy from individual cancer patients. The cells were then genetically modified with an adenoviral vector (CG-06444) encoding the human GM-CSF gene. They were irradiated, frozen and then administered to patients as a series of five intradermal vaccinations, every 2 weeks. The primary end point was overall survival. Unfortunately, the study was closed prematurely due to technical limitations in manufacture of vaccine.

At the 11th World Conference on Lung Cancer, Schiller and colleagues reported results of a Phase II randomised trial of GM-CSF gene-modified autologous tumour vaccine (CG-8123) with and without low-dose cyclophosphamide in advanced-stage NSCLC. Patients with successful vaccine manufacturing were randomised to vaccine alone (every 2 weeks for five times) or to vaccine plus immunomodulatory doses of cyclophosphamide (250 mg/m² 1 day prior to vaccine dose one, three and five). Ninety-seven patients

Table 1. Competitive environment: clinical trials with vaccines for lung cancer therapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Vaccine/trial phase</th>
<th>Number of patients*</th>
<th>Immune cell or medium</th>
<th>Best response†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salgia et al.</td>
<td>GVAX/Phase I</td>
<td>34</td>
<td>Autologous tumour cells</td>
<td>SD in 5 patients</td>
</tr>
<tr>
<td>Nemunaitis et al.</td>
<td>GVAX/Phase II</td>
<td>43</td>
<td>Autologous tumour cells</td>
<td>CR in 3 patients</td>
</tr>
<tr>
<td>Morris et al.</td>
<td>α(1,3) galactosyl-transferase</td>
<td>7</td>
<td>Allogeneic tumour cells</td>
<td>SD in 4 patients</td>
</tr>
<tr>
<td>Morris et al.</td>
<td>B7.1 (CD80)/Phase I</td>
<td>19</td>
<td>Allogeneic tumour cells</td>
<td>PR in 1, SD in 5 patients</td>
</tr>
<tr>
<td>Hirschowitz et al.</td>
<td>DC/Phase II</td>
<td>16</td>
<td>Dendritic cells</td>
<td>Immunological response: 5 tumour antigen-independent response and 6 antigen-specific response</td>
</tr>
<tr>
<td>Horig et al.</td>
<td>ALVAC-CEA/B7.1/Phase II</td>
<td>3</td>
<td>Recombinant, poxvirus-based vaccine</td>
<td>Phase I: no clinical response in NSCLC patients</td>
</tr>
<tr>
<td>Palmer et al.</td>
<td>BLP25 (MUC1)/Phase I</td>
<td>17</td>
<td>MUC1 antigen</td>
<td>SD in 4 patients</td>
</tr>
<tr>
<td>Oka et al.</td>
<td>WT1/Phase I</td>
<td>10</td>
<td>WT1 peptide</td>
<td>Decreased tumour markers in 3 patients</td>
</tr>
<tr>
<td>Krug et al.</td>
<td>Fucosyl GM1-1KLH conjugate/Phase I</td>
<td>16</td>
<td>GM1 peptide</td>
<td>8 patients mounted IgM responses of ≥ 1:80. Six patients remained alive (or lost follow-up) at 9,16,18, 22, 31 and 32 months</td>
</tr>
<tr>
<td>Salazar et al.</td>
<td>HER-2/neu/Phase I</td>
<td>1</td>
<td>Her-2/neu peptide</td>
<td>-</td>
</tr>
<tr>
<td>Brunsvig et al.</td>
<td>GV1001 and HR2822/Phase II</td>
<td>26</td>
<td>Telomerase peptides</td>
<td>Immunological response: 13 patients. One complete tumour response</td>
</tr>
<tr>
<td>Atanackovic et al.</td>
<td>MAGE-3/Phase II</td>
<td>17</td>
<td>MAGE-3 protein</td>
<td>-</td>
</tr>
<tr>
<td>Gonzalez et al.</td>
<td>DC/Phase II</td>
<td>40</td>
<td>EGF protein</td>
<td>90% of all vaccinated patients seroconverted. GAR, n = 19. At 6 months, 12 patients had clinical and radiological SD. Survival improved in GAR</td>
</tr>
<tr>
<td>Gabrilovich et al.</td>
<td>EGF/Phase II</td>
<td>22</td>
<td>Infected with adenovirus (wild-type p53)</td>
<td>5 SD; response to chemotherapy postvaccination (in 13 patients); PR in 7, SD in 2 patients</td>
</tr>
<tr>
<td>Grant et al.</td>
<td>BEC2-BCG /Phase II</td>
<td>15</td>
<td>Anti-idiotypic against GD3</td>
<td>-</td>
</tr>
<tr>
<td>Giaccone et al.</td>
<td>BEC2-BCG /Phase III</td>
<td>257</td>
<td>Anti-idiotypic against GD3</td>
<td>No survival benefit</td>
</tr>
</tbody>
</table>

*Number of patients with lung cancer in the trials listed.
†Clinical or immunological responses.
CR: Complete response; GAR: Good antibody responders (antibody titre > 1:4000 and at least 8x the preimmunisation value); NSCLC: Non-small-cell lung cancer; PR: Partial response; SD: Stable disease.
underwent tumour harvest. The success rate of vaccine manufacture was 75% for solid tumours processed and 63% for pleural effusions. Interim analysis of the first 27 patients revealed a median survival of 4.5 months for the vaccine-only treatment arm, and 11.9 months for the cyclophosphamide plus vaccine arm. The difference was not statistically significant; however, these results can be explained due to the small sample size [57].

5.1.2 BLP25 (MUC1)
Cancer-associated mucins are another potential target for immunotherapy. These molecules are thought to promote metastases by facilitating adhesion of malignant cells to the endothelial cell surface. They exhibit unique glycosylation patterns, making them tumour-specific immunogens [26]. The use of a mucin 1 (MUC1)-derived peptide for the treatment of stage III/IV NSCLC was studied in a Phase I trial that included 17 patients [58]. Previous preclinical studies showed activity of liposomal vaccines targeting the mucinous carcinoma-associated glycoprotein MUC1. The study tested safety and tolerability of two different vaccine doses (20 and 200 µg, respectively), along with a coadministration of immunomodulatory doses of cyclophosphamide (300 mg/m²) given 3 days prior to vaccination. The patients received subcutaneous injections at weeks 0, 2, 5 and 9. Immunological response was measured based on antibody production, CTLs and proliferative T helper (Th1) cell response. Out of 17 patients, 12 completed the vaccination protocol and were evaluable for response. Generation of CTLs against MUC1-positive tumour cell lines was seen in 5 (42%) out of 12 evaluable patients. No significant humoral and objective antitumour responses were seen. Four patients (33%) achieved stable disease. Median survival was 5.4 months in the 20-µg group and 14.6 months in the 200-µg group. There was no significant haematological toxicity other than a clinically insignificant grade 3 lymphopenia (one patient in each group); nonhaematological toxicities were mild and self-limited. The liposomal vaccine was well tolerated and appeared to elicit a cellular immune response rather than a humoral response in NSCLC. A randomised Phase II trial of MUC1 peptide vaccine versus best supportive care was subsequently developed as a second-line therapy for advanced NSCLC. This completed accrual of a planned 168 patients in November 2002 [59]. Patients with stages IIIIB or IV NSCLC were randomised to either best supportive care or best supportive care plus MUC1 vaccination following standard chemotherapy or radiation if they had achieved stable disease. The vaccine arm consisted of a single dose of cyclophosphamide 300 mg/m² i.v. followed by eight weekly subcutaneous injections with MUC1 vaccine (L-BLP25) containing 1-mg antigen. Maintenance immunisations were given at 6-week intervals. A total of 171 patients were randomised. Follow up was at 2 years after completion of enrolment. The median survival was 17.2 months in the vaccine arm versus 13.0 months in the best supportive care arm (p = 0.1802). Stratification of patients for stage IIIIB with or without effusion was performed, and median survival for stage IIIIB without effusion on the vaccine arm was not reached (n = 35), while the median survival for the same group on best supportive care was 13.3 months (p = 0.0924). For stages IIIIB (with effusion) and IV, the difference was 15.1 versus 12.9 months, respectively (p = 0.6931). This preliminary analysis suggests that MUC1 vaccination may have an effect on survival in a selected subgroup of patients with NSCLC; however, the data did not reach statistical significance. This approach (combination of low-dose chemotherapy with a vaccine) remains very interesting in several different malignancies and needs to be explored further.

5.1.3 Dendritic cell immunisations
A Phase I clinical trial enrolled 16 individuals with stage IA - IIIIB NSCLC treated with surgery, chemoradiation or multimodality therapy to receive dendritic cell vaccine [60,61]. Previously treated NSCLC patients were immunised intradermally 1 month apart. Immunological responses measured by enzyme-linked immunosorbent spot (ELISPOT) for IFN-γ followed three distinct patterns of reactivity: i) 5 of 16 patients showed no clear immunological response; ii) 5 of 16 patients showed a tumour antigen-independent response; and iii) 6 of 16 showed an antigen-specific response. Immunological responses were independent of stage and prior therapy. Unfortunately, clinical outcomes were also independent of measured immunological responses like in many other immunotherapy trials.

5.1.4 B7.1 (CD80)
We believe that the most potent combination of tumour-specific antigens may be delivered by an allogeneic whole-cell-based vaccine, targeting all the ‘shared’ tumour-specific antigens. This may elicit a polyvalent CTL response with many clonal specificities preventing tumour evasion by antigenic modulation. To test this hypothesis, the authors’ group developed an allogeneic lung cancer vaccine expressing the costimulatory molecule B7.1 [53]. One hypothesis is that liberation of antigen due to activation of the innate immune response (NK) and lysis of the vaccine cells mediates local inflammation, which will attract dendritic cells that uptake the antigen and the killed vaccine cells and cross-present the tumour-associated antigens through patient MHC to generate tumour-specific CTL. To test this hypothesis a Phase I trial for advanced-stage (IIIIB/IV) NSCLC patients using an allogeneic NSCLC tumour cell line (AD100) transfected with B7.1 (CD80) and HLA A1 or A2 was conducted at the University of Miami [62] to study the generation of specific CTL and clinical response. Patients with NSCLC were vaccinated intradermally three times, once every 2 weeks (one course) for a maximum of three courses. Out of 19 patients, 18 were evaluable, 4 patients experienced minimal skin erythema, and there were no serious adverse events associated with the vaccine. All but one patient had a measurable CD8 response after three immunisations, as
measured by the release of IFN-γ in ELISPOTs. The immune response of six surviving, clinically responding patients shows that tumour vaccine-specific CD8 titres to B7.1 vaccine continue to be elevated for at least up to 38 months. Overall, one patient had a partial response and five patients had stable disease. The median survival for all patients at the time of publication was ≥ 18 months with corresponding estimates of 1-, 2- and 3-year survivals of 52, 30 and 30%, respectively, for historical age-matched controls. As of March 2006, three of the five patients who achieved stable disease and the patient who achieved partial response are still alive with survivals ranging from 36 to ≥ 63 months. One of the patients who achieved stable disease experienced progression of disease after 2 years, and was revaccinated. This patient was able to regain stable disease again for another year without need of palliative chemotherapy. None of the 13 patients who did not respond to the vaccinations are alive. This study showed that the B7.1 whole-cell vaccine could induce a moderate to strong CD8 allogeneic response with minimal toxicity. The unexpectedly long survival suggests a clinical benefit from vaccination. These results warranted further investigation as this was a small cohort, single-institution study. Furthermore, antigenic determinants in NSCLC recognised as a result of alloimmunisation have not yet been defined. In this context, two Phase II trials are planned at the University of Miami with the B7.1 vaccine. The aim of the first study is to determine whether patients with early stage NSCLC can develop CTL responses to the autologous tumour after surgery and adjuvant chemotherapy leading to improved disease-free survival. A second trial, in patients with advanced NSCLC (who had responded to palliative chemotherapy and are in remission or with stable disease) is planned in order to evaluate whether the CTL response to vaccination is associated with an increased progression-free survival.

5.1.5 ALVAC/B7.1
ALVAC, a nonreplicating canary poxvirus-based vaccine, was studied in combination with B7.1 costimulatory molecule on tumour cells expressing CEA in a Phase I clinical trial [63]. This study represented the first use of costimulatory ligands to enhance antitumour response in cancer patients. Three cohorts were treated with increasing doses of ALVAC-CEA-B7.1 vaccine. Patients who had metastatic adenocarcinoma-expressing CEA were vaccinated every 4 weeks for 3 months. Only 3 out of 18 patients enrolled in the study had adenocarcinoma of the lung. Three patients (one with pancreas cancer and two with colon cancer) who showed stable disease underwent repeated vaccination, which resulted in augmented CEA-specific T-cell responses. The highest dose was delivered without evidence of significant toxicity or autoimmune disorders. The study concluded that CEA-specific T-cell responses could be elicited with repeated vaccinations, and that B7.1 may improve the immunological response to vaccination against tumour-associated antigens. This poxvirus-based vaccine is being tested in Phase II clinical trials at present in patients who have cancer cells that express CEA [64].

5.1.6 WT1
Oka et al. evaluated immune response in patients vaccinated with Wilms tumour protein (WT1), a protein overexpressed in leukaemias and several solid tumours including lung cancer [65]. This vaccination strategy was tested in 26 patients (10 with lung cancer). The patients received HLA-A*2402-restricted, natural or modified 9-mer WT1 peptide combined with Mon tanide ISA51 adjuvant. This study reported decreased tumour markers in 3 of 10 patients with lung cancer, and this is one of the few immunotherapy trials that identified a correlation between clinical response and antitumour CD8+ T-cell activity. One of the responders continued to receive the treatment for 2 years without significant adverse effects.

5.1.7 MAGE-3
Melanoma-associated antigen (MAGE)-3 protein, an antigen originally identified in melanoma, is also expressed in some lung tumours and has also been studied as a vaccine target. A Phase II trial using MAGE-3 protein was evaluated in the adjuvant setting to treat high-risk NSCLC patients [66]. The objective was to analyse the induction of MAGE-3-specific CD4+ T-cells in patients with NSCLC. Seventeen patients with stages I or II NSCLC who expressed MAGE-3 were enrolled. All patients underwent surgical resection and had no evidence of disease. The first nine patients received MAGE-3 protein alone; the following eight patients received MAGE-3 protein combined with AS02B adjuvant. Patients received four intradermal injections (protein alone cohort) or four intramuscular injections (protein with adjuvant) at 3-week intervals (days 1, 22, 43 and 64). In the first cohort, three patients developed a modest, but significant, increase in antibodies against MAGE-3 protein. In the second cohort, seven out of eight patients developed marked increase of antibodies. All 17 patients were examined for CD4+ T-cell response. In the first cohort (no adjuvant), only one patient showed a CD4+ T-cell response against the specific tumour antigen. In the other group, all four of them showed a marked increase in CD4+ T-cell responses against MAGE-3.DP4. Thus, the vaccination with the recombinant protein of a cancer testis antigen provided a strong antigen-specific CD4+ T-cell response along with antibodies and CD8+ T-cell responses. A multi-centre Phase II randomised trial is comparing MAGE-3 versus placebo as adjuvant therapy for completely resected MAGE-3+ stages IB and II NSCLC. The treatment schedule consists of an induction phase with vaccination every 3 weeks, five times (beginning at 4 – 8 weeks postsurgical resection) followed by eight maintenance vaccinations at 3-month intervals. The first results of this study, which is underway at 48 centres in Europe were presented in the ASCO 2006 Meeting in Atlanta, Georgia [67,68]. Patients with stage IB or II NSCLC completely resected were blindly randomised for vaccination or placebo. Vaccination was started > 6 weeks...
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after surgery, with five vaccinations at 3-week intervals, followed by eight vaccinations every 3 months. This study confirms expression of MAGE-A3 antigen in 35% of early NSCLC cases, and demonstrates good tolerability of postoperative MAGE-A3 vaccination. The recurrence rate was 30.3% in the vaccinated group and 41.7% in the placebo group (p = 0.138); no difference in relapse rate was seen in stage IIB (30.5 versus 33.3%); an important difference was seen in stage II patients (30 versus 57%; p = 0.55) [68].

5.1.8 Other vaccine strategies for NSCLC

In the 2005 ASCO meeting, a Phase I/II clinical trial, which involved a combination of telomerase peptides GV1001 and HR2822, was presented [69]. Twenty-six patients with advanced NSCLC were vaccinated with intradermal injections of GV1001 in combination with HR2822 and GM-CSF. Out of 24 evaluable patients, 11 had an immune response against GV1001 following the primary vaccination regimen, and response was detected in two additional patients following booster injections. The treatment was well tolerated, with minor side effects. There was a complete tumour response in one patient who developed GV1001-specific CTL. The study demonstrated the feasibility and efficacy of telomerase vaccination for the treatment of resistant NSCLC patients. Because telomerase expression is seen in many tumour types, this may represent a broadly applicable vaccine approach.

A Phase I clinical trial supported by the National Cancer Institute was conducted to assess the safety and feasibility of antitumour vaccination in advanced NSCLC patients using α(1,3) galactosyltransferase [70]. Three irradiated genetically altered human lung cancer cell lines engineered to express xenotransplantation antigens by retroviral transfer of the murine α(1,3) galactosyltransferase gene were intradermally injected (there was a dose escalation per cohort) every month for four cycles. As of May 2005 when the results were presented in the meeting, seven patients had been treated. The most common reported adverse events were injection site pain, local skin reaction, fatigue and hypertension. Four patients attained stable disease for > 16 weeks (range 17 – 28) and three others had disease progression. The study concluded that this vaccination is safe and feasible in NSCLC.

Pooled data from two pilot clinical trials conducted by Gonzalez and colleagues were presented in a review [71]. Both trials were open-label randomised studies, intended to compare safety and immunogenicity of vaccination with an EGF-based vaccine when two different adjuvants (aluminum hydroxide or montanide ISA 51) were used. In the first study, 20 patients received an intramuscular vaccine on days 0, 7, 14, 21 and 51. In the second study, an additional 20 patients were randomised and vaccinated as in the first study, but all received a single dose of cyclophosphamide 200 mg/m² 3 days prior to vaccination. The results of both pilot trials showed that montanide increased the percentage of good antibody responders (GAR), and cyclophosphamide prevaccination did not improve antibody response. There was a significant increase in survival for patients with maintained antibody response. In the GAR subgroup, the antibody titres appeared to show some correlation with survival.

Her-2/neu-derived peptides have also been studied as a vaccine in a Phase I trial in breast and lung cancer [72]. A minority of patients immunised with the Her-2/neu-derived multi-peptide vaccine developed a Her-2/neu peptide-specific T-cell immunity or antibody immunity, and none developed Her-2/neu protein-specific immunity. This study included only one patient with stage III NSCLC. Another randomised Phase II trial comparing EGF vaccination versus best supportive care is ongoing now [71].

Lucanix™ (NovarX) is a nonviral gene-based allogeneic tumour cell vaccine that demonstrates enhancement of tumour antigen recognition as a result of TGF-β inhibition; a randomised dose-variable Phase II trial involving stage IIIIB/IV NSCLC was presented at ASCO 2006 [73]. Each patient received one of three doses (1.25, 2.5 and 5.0 x 10⁷ cells/injection) given intradermally, to a maximum of 16 injections either monthly or every other month. Immune function, safety and anticancer activity were monitored. Sixty-one patients received a total of 417 vaccinations. No significant (higher than grade 3) adverse events probably or definitely associated with administration of the vaccine were observed. A dose-related survival difference was demonstrated in patients who received > 2.5 x 10⁷ cells/injection versus those who received < 2.5 x 10⁷ cells/injection (p = 0.0151). The percentage of patients surviving 1 and 2 years was 61 and 52%, respectively, for the high-dose group and 40 and 13%, respectively, for the low-dose group; 15% of patients achieved a partial response. Cytokine production (IFN-γ, p = 0.006; IL-6, p = 0.004; IL4, p = 0.007) was induced, antibody mediated response to vaccine HLA antigen was observed (p = 0.014) and cell-mediated response showed a correlation trend (p = 0.086) in patients achieving stable disease or partial response (15%) compared with those with progressive disease.

Gp96 is a member of heat-shock proteins family. It is an endoplasmic reticulum resident and a chaperone for endogenous peptides and larger protein fragments destined for MHC class I and II loading. Gp96-Ig fusion protein is secreted from transfected cells. In murine studies, tumour-secreted gp96-Ig induces specific CD8 CTL expansion, and, when used as a vaccine, mediates tumour rejection and long-lasting tumour immunity by CD8+ cells independent of CD4+ cells. Optimal CD8 activation requires IFN-γ, CD28 and B7, but is independent of CD40L. A Phase I clinical trial using an allogeneic gp96-Ig transfected lung cancer cell line is planned to start soon at the University of Miami for the treatment of patients with metastatic disease or relapsed NSCLC who have failed at least two lines of palliative therapy. Early studies with gp96 isolated from human tumours have already provided encouraging results in human trials [74,75].
5.2 Clinical trials for small-cell lung cancer
BEC-2–BCG is probably the best-known vaccine for SCLC; unfortunately, as mentioned before, the large randomised Phase III trial done with the vaccine did not show any difference in survival compared with placebo in patients with SCLC that have completed chemotherapy and radiation [51]. Here, other attempts to induce immune response in patients with SCLC are briefly presented.

5.2.1 Dendritic cell-based immunisations
DCVax® (Northwest Biotherapeutics), another dendritic cell-based immunotherapy, is an active immunisation platform developed for the potential therapy of several malignancies, including NSCLC, renal, glioblastoma multiforme and hormone-refractory prostate cancer [76]. DCVax platform is tailored to a specific cancer type using either purified tumour-specific antigen or tumour cell extract from the patient at the time of surgical resection. At the 2005 ASCO meeting, Gabrilovich and colleagues reported their initial results of a Phase II ongoing trial, which involved 22 patients with extensive SCLC. Those patients who attained stable disease or minor progression after first-line chemotherapy underwent leukapheresis 8 weeks after the last dose of chemotherapy and dendritic cells were expanded ex vivo. Dendritic cells were transfected with an adenoviral construct containing wild-type p53. Patients received three intradermal injections (2 – 5 x 10⁶ p53+ dendritic cells/dose); 5 patients had stable disease, 17 patients had progression of disease and 11 out of 20 patients had an immunological response. Patients who progressed received second-line chemotherapy. An analysis of clinical responses in 13 of the progressing patients revealed 7 patients with partial remission, 2 patients with stable disease and 4 patients with documented progression of disease. The authors conclude that the dendritic cell vaccine was safe and well tolerated; moreover, the vaccine induces a substantial immune response to the vaccine and may sensitise SCLC tumours to subsequent chemotherapy due to the results seen [77].

5.2.2 Fucosyl-GM1–KHL conjugate
A synthetic version of fucosyl GM1 conjugated to keyhole limpet haemocyanin (KHL) was studied in a Phase I clinical trial in patients with SCLC following a major response to standard therapy [78]. Patients with limited or extensive disease SCLC (n = 16) who completed initial treatment with chemotherapy (and radiation if indicated) were enrolled. Three dose levels of fucosyl-GM1–KHL conjugate were studied. QS-21 was used as adjuvant. Vaccinations were administered intradermally on weeks: 1, 2, 3, 4, 8 and 16. No grade 3 or 4 toxicities were observed. Five of six patients at a 30-µg dose level and three out of five patients at a 10-µg dose level mounted IgM responses of ≥ 1:80. Antibodies were confirmed by flow cytometry in seven out of eight patients. None of the patients in the lowest dose level had titres > 1:80. This suggested a dose-response with 10 and 30 µg. A Phase II clinical trial using a tetravalent vaccine approach has been planned by the authors in which fucosyl GM1 will be combined with vaccines against three other antigens: GM2, Globo H and polysialic acid in patients previously treated for SCLC.

6. Current research goals
Several considerations are germane to development of immune therapies for cancer:

- There is a need for new therapeutic modalities for the treatment of lung cancer, and immunotherapy represents an attractive option. We need to identify if the induction of immune response with an autologous vaccine is the best approach in comparison with the more practical one offered by allogeneic vaccines.
- Whole-cell-based vaccines may offer an advantage until specific antigens are identified for lung tumours.
- Success of immune approaches will in part be governed by interactions between the tumour and the host immune system. Tumours may tolerate the adaptive immune system and may blunt innate responses as well. As we learn more about the intricate interactions between tumours and the immune system, we will continue to improve on our ability to evoke responses against tumour antigens.
- We still do not know how best to harness cytokines and chemokines in fashioning response. As we understand more about the role of cytokines in T-cell development and activation of immune effector cells, we will improve our ability to amplify desirable responses appropriately.
- The role of T-reg in suppressing antitumour immune response needs to be better defined. Depletion of T-reg may facilitate improved responses and selective depletion is rapidly becoming feasible.
- Future approaches involving the use of immunotherapy include combinations with traditional cytotoxic agents as well as antiangiogenic agents. Chemokine-mediated tolerance mechanisms and immunogenicity mechanisms may also deserve consideration. Appropriate integration of immune therapy into existing treatment paradigms will improve outcomes.

7. Scientific rationale
In general, cancer vaccines incorporate tumour antigens and adjuvant molecules to facilitate tumour antigen recognition by the immune system. The antigens can be whole autologous or allogeneic cells, specific peptide epitopes or proteins. In the case of lung cancer like most other cancers, the most important tumour-associated antigens have not been identified. Many immunotherapy approaches involve gene therapy, in which a specific gene is transferred to the relevant cell by a vector that is generally virus like (e.g., retrovirus or adenovirus); however, nonviral vaccines such as liposomes and cellular vaccines are also in development.
Dendritic cells are the most effective antigen-presenting cells (APCs) thus far identified and play a major role in inducing primary and secondary T-cell immune responses against cancer in vivo. Dendritic cells are capable of stimulating immunologically naive T cells [79,80]. The cytokine GM-CSF induces differentiation of bone marrow-derived cells into APCs (macrophages and dendritic cells). A recent vaccine involving GM-CSF gene-transduced tumour cells is called GVAX. In this example, transfection of autologous tumour cells with the GM-CSF gene has shown induction of cancer-specific antitumour immunity requiring both CD4+ and CD8+ cells mediated through dendritic cell stimulation [81,82]. Cancer patients may have defects in macrophage and dendritic cell antigen presentation to T cells. Antitumour immunity in these trials has been measured by delayed-type hypersensitivity, by antitumour response in tumour samples and by clinical responses [54,55,83,84].

Another approach involves transduction of tumour cells with costimulatory molecules. In the B7.1 vaccine, the costimulatory molecule B7.1 (CD80) has been introduced into an allogeneic vaccine to induce T- and N K-cell responses against tumour cells [62]. Tumour cells transfected with B7.1 and HLA molecules have been shown to stimulate an avid immune response by direct antigen presentation and activation of T cells, in addition to allowing cross presentation [85-88]. An important difference between allogeneic B7.1 vaccine and autologous vaccines such as GVAX is the early activation of N K cells and the innate arm of the immune system due to mismatched MHC.

Whole-cell vaccines have a general advantage because of their ability to induce a polyvalent-response type against many epitopes, in contrast to a vaccine directed at a single or few epitopes that may have limited use due to evolution of tumour escape mutants [89]. If vaccination is successful and CTLs are generated, the responsible antigens can be identified later.

Allogeneic cell-based vaccines offer an alternative to autologous vaccines. These vaccines are predicated on the assumption that lung tumour antigens are shared between patients, and such antigens can be ‘cross-presented’ by patients’ APCs. Although there is only limited evidence for shared antigens in lung tumours [88,90], shared antigens have been observed in other cancers [91,92]. Manufacture of autologous vaccines is difficult due to the fact that tumour specimen is needed, and frequently patients have to undergo a second surgical procedure (core biopsy) to acquire autologous tissue making allogeneic approaches more attractive. In one study < 60% of the patients scheduled to receive the autologous vaccine GVAX actually received the vaccine due to technical hurdles [55].

BEC2 was interesting because it is an anti-idiotypic vaccine that targets the ganglioside GD3 expressed on cells of neuroendocrine origin, including SCLC cells. It targets the binding region of the mouse monoclonal antibody R24, which binds to ganglioside GD3. Hence, BEC2 elicits an immune response against GD3 [93]. A different mechanism of action is exerted by BLP25 vaccine, which is a liposomal preparation of the carcinoma-associated mucin MUC1. MUC1 is expressed on the cell surface of many common adenocarcinomas, including lung, breast, pancreas, prostate, ovary and stomach. Cancer-associated mucins are linked to the development of metastases through promotion of the adhesion of malignant cells to the endothelial cell surface. In addition, they exhibit uncommon glycosylation patterns, and hence, become useful immunogens [94]. Autologous dendritic cell vaccines generated from CD14+ precursors have also been tested as an alternative approach. Other investigators have considered use of dendritic cells that are pulsed with apoptotic bodies of an allogeneic NSCLC cell line (1650 TC), which overexpressed Her-2/neu, CEA, WT1, MAGE-2 and Survivin [95].

8. Potential development issues

The development of lung cancer vaccines is very challenging. Despite multiple clinical trials including Phase I, II or even III trials, approval of any vaccine for cancer has yet to be achieved. The authors have commented more extensively in the text and in Section 10 on logistical and scientific problems for vaccine therapy. For example, the fact that there is not a well-identified antigen in lung cancer makes the process of development a lung cancer vaccine very challenging. How can we make a good vaccine if we are not sure which antigen is really the target? In addition, we still need to find the best strategy to generate immune responses; for instance, the use of low-dose chemotherapy in conjunction with a vaccine, as was done in the case of the MUC vaccine [58,59], remains an interesting approach. There exists literature that proposes B-cell immunosuppression as a way to enhance the TH1 T-cell immune response. In the case of B7.1, ways to enhance the immune response against the vaccine are being investigated [62]. One of the options contemplates combination with low-dose chemotherapy or combinations with targeted agents in both cases with the goal to deplete B-cell immunity, as it has been done with other vaccines.

There are many logistical problems, including the fact that there is not much interest from pharmaceutical companies to invest in lung cancer vaccines; the number of lung cancer vaccine trials is minimal compared with the number of chemotherapeutic trials ongoing. In that regard, for example, National Institutes of Health grants in the U.S or grants from private agencies are used to finance the development of the vaccines, but these funds can never match the investment power of the pharmaceutical industry.

9. Conclusion

The relatively new field of immunotherapy for lung cancer is evolving rapidly. The identification of potential antigenic targets and increased understanding of the immune mechanisms have led to a series of novel strategies for generating antitumour immunity against lung cancer. Despite the difficulties seen in the generation of antitumour response in lung cancer,
several agents have already been shown to be capable of priming immune responses in clinical trials, and some have demonstrated a promising clinical antitumour activity. These strategies hold promise for improving the survival of patients with lung cancer.

10. Expert opinion

Immune therapy presents an attractive, but unproven, addition to the antitumour armamentarium. However, results from several clinical trials show only modest success. Improvements are needed to better define tumour antigens and select adjuvants, and capitalise on known immune mechanisms to boost the response against tumour cells. It has been thought that NSCLC evades the immune response by avoiding or suppressing the priming of T cells. A better understanding of the different mechanisms involved in the immune system regulation, as well as new advances in modulation, have challenged this concept, and research in this field is progressing rapidly.

Several factors such as wide variability of the final vaccine product, different sources of APCs used (dendritic cells versus tumour cells), different techniques of preparation, different sources of tumours used (autologous versus allogeneic), the inclusion of cytokine-producing DNA (human or viral) and unknown potent 'immunogenic' antigens have made selection of optimal approaches and evaluation of outcomes quite difficult. Clearly, challenges facing this new approach include standardisation of the technology, and the difficulty in correlation of immune response to desired clinical outcomes.

Although several preclinical trials have suggested antitumour activity, a small number of clinical trials using various vaccine strategies have been developed in lung cancer. These trials have shown some evidence of induction of immune responses and suggested clinical benefit. Responses to immunotherapy may be delayed, and occasionally, an increase in tumour size may reflect an inflammatory reaction rather than tumour progression or therapy failure. In this regard, other clinical parameters such as time to progression or survival can be considered for future trials instead of the classic Response Evaluation Criteria In Solid Tumours (RECIST) criteria, which are used to evaluate the solid tumour response, which is based solely on changes in tumour diameter.

Reducing large tumour burden with immunotherapy alone is very unlikely. Vaccination may be best adapted to the adjuvant setting after patients have achieved 'clinical remission' with surgery or chemotherapy and radiation, where cancer vaccines may help to control microscopic disease. Because even the smallest lung tumours (stage IA) still have a high mortality rate, with only ≈70% of the patients alive at 5 years from diagnosis, integration of immune approaches in the adjuvant setting may be very beneficial. Because most patients diagnosed with advanced-stage disease (70 – 80% of all NSCLC patients) receive only a limited course of adjuvant chemotherapy (four to six cycles), which is not curative, immune therapies may be used to help 'maintain' a disease-free state by targeting microscopic residual disease in patients at high risk for relapse. Several interventions other than chemotherapy, including tyrosine kinase inhibitors, are being tested in this setting and certainly vaccinations represent an attractive alternative.

Bibliography

Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.


Present and future of lung cancer vaccines


• Randomised Phase III trials that showed equivalent response and toxicity among third-generation chemotherapy agents.


• One of the largest NSCLC trials that showed superior survival of docetaxel against vinorelbine once they are combined with cisplatin.


• Another Phase III trial comparing the third-generation chemotherapy agents for NSCLC.


• First trial with tyrosine kinase inhibitors that showed survival benefit in NSCLC.


• Very important meta-analysis that suggested use of chemotherapy in NSCLC.


• Large randomised trial that showed the benefit of chemotherapy compared with standard of care.


• Two third-generation chemotherapy agents are better than one.


• Benefit of chemotherapy seen is limited to four cycles.


**No benefit in survival was found with the use of BEC2/BCG in NSCLC after standard chemotherapy and radiation.**


**Vaccination with GM-CSF is promissory and safe in NSCLC patients.**


**Data from a randomised Phase II study with GM-CSF presented in the World Lung Cancer Congress.**


Present and future of lung cancer vaccines


61. Very interesting data showing benefit for patients with stage IIIB NSCLC.

62. HEGE KM, CARBONE DP: Lung cancer vaccines and gene therapy for NSCLC.


64. ERTL HC: Technology evaluation: Vaccine-induced immune responses.

65. Important review of the topic of lung cancer vaccines and gene therapy for NSCLC.


67. Dendritic cell vaccines shows a potential role in NSCLC.


70. First human trial showing safety with this new B7.1 vaccine.


Website
2/search.pl#results
National Cancer Institute. SEER incidence rates, age-adjusted and age-specific rates by age & sex (small cell lung and bronchus).

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