Review

Therapeutic vaccines for ovarian cancer

John B. Liao, Mary L. Disis,

HIGHLIGHTS

• Completed phase 2 and 3 trials with clinical endpoints have demonstrated modest responses.
• Targeting the immunosuppressive tumor microenvironment may augment the effectiveness of the next generation of vaccines.

ARTICLE INFO

Article history:
Received 17 May 2013
Accepted 17 June 2013
Available online 22 June 2013

Keywords:
Ovarian cancer
Vaccines
Immune therapies

ABSTRACT

While therapeutic vaccines for ovarian cancer represent only a small fraction of active clinical trials, growing interest in this area and the accumulated data supporting the use of vaccines in cancer treatment portend further expansion of trials incorporating these strategies. This review explores the rationale for the use of vaccines for the treatment of ovarian cancer. It examines vaccine platforms that have been investigated and reviews the data from these studies. We also highlight recently reported phase 2 and 3 clinical trials with clinical outcomes as endpoints. Finally, we consider directions for the next generation of vaccines in light of these findings and our emerging understanding of agents that may augment vaccine responses by targeting the immunosuppressive impact of the tumor microenvironment.

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Introduction

A survey of clinicaltrials.gov in March 2013 reveals that of all currently open and recruiting clinical trials for ovarian cancer patients, between 5 and 10% of studies evaluate approaches using immune based therapies. Approximately 40% of clinical trials involving modulation of the immune system employ a vaccine alone or in combination with other agents. While immuno-oncology represents but a small fraction of all open clinical trials for ovarian cancer, growing interest in this area and the accumulated data supporting the use of vaccines in cancer treatment, portends further expansion of trials incorporating these strategies. This article will review the rationale for the use of vaccine therapy in ovarian cancer, outline vaccine design considerations as we survey a sample of current and recent applications under investigation, and consider future directions for the field.

What is the rationale for vaccine therapy in ovarian cancer?

Ovarian cancer is immunogenic. The ability of the immune system to recognize ovarian cancer is associated with improved prognosis. The form of immunity associated with this improved prognosis is known; T cell infiltrates in ovarian cancers are shown to be associated
with improved prognosis in a number of studies. The infiltration of T cells has been observed in ovarian cancers since 1982 [1]. The full prognostic significance of T-cell infiltration in ovarian cancers, that it rivalled optimal surgical cytoreduction, was subsequently reported by Zhang et al in 2003 [2]. The presence of intratumoral T cells was an independent prognostic factor for DFS and OS by multivariate analysis. These findings have been validated in several subsequent studies, and point to the specific importance of cytotoxic CD8+ T-cells [3–9]. Regulatory T cells, another subset of T cells that can modulate immune responses and maintain tolerance to self-antigen, have been shown to predict poor patient survival in ovarian cancer [6,10].

The natural history of ovarian cancer also allows opportunities for therapeutic vaccines to be applied. Although over 60% of women diagnosed with ovarian cancer will have distant metastases according to the most recent NCI SEER data, response rates to initial chemotherapy and cytoreductive surgery can be as high as 85% [11]. Unfortunately, despite these initial responses, over two thirds of patients will recur and even in patients who achieve complete remissions, maintaining these has proven elusive [12]. Despite advances in therapies, cure rates have changed little and most patients can expect a relapsing and remitting clinical course of progressive resistance to chemotherapies. However, periods of remission could allow vaccines the necessary time in patients with low disease burdens to induce an effective antitumor response to prolong remissions and prevent recurrences.

Finally, we have already seen the ability of novel therapies, modulating T-cells, demonstrate responses in ovarian cancer patients. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) engagement of costimulatory molecules can result in the arrest of T cell responses and impaired antitumor response. When antibody blockade of CTLA-4 was used in heavily pretreated ovarian cancer patients, who had received multiple lines of chemotherapy, four of nine patients were able to achieve stable disease, by CA-125 and radiographic criteria, without significant toxicities [13,14]. Programmed death 1 (PD-1) is another T-cell coinhibitory receptor. Antibody blockage of its ligand, PD-L1, has been studied in patients with selected advanced cancers, including ovarian cancer. Patients with advanced or metastatic disease having failed at least one line of chemotherapy were treated with anti-PD-L1 antibody in an effort to block inhibitory signals on effector T cells. 18% of ovarian cancer patients (n = 17) were able to achieve stable disease for at least 6 months [15]. The success of these recent methods of T cell modulation in an antigen non-specific fashion, in pretreated patients, suggests that vaccines capable of generating focused immune responses specifically targeting tumor antigens may be even more effective.

What is the track record of ovarian cancer vaccine therapy?

An ideal antigen for an ovarian cancer therapeutic vaccine would be solely expressed on ovarian cancer cells, be highly immunogenic with a bias toward a cytotoxic antitumor response, and be able to be carried or expressed using the chosen vaccine platform. Additionally, the target should be biologically necessary in maintaining the malignant phenotype so that tumor cells cannot escape immune targeting through loss of expression. These would be considered tumor specific antigens. Few, if any, candidate antigens will meet all these criteria. HPV oncoproteins E6 and E7 in cervical cancer are one of the few examples of this, viral proteins that are also required for the malignant phenotype. For most malignancies, vaccine targets represent tumor-associated antigens, which are over expressed in tumor cells, but also are present in lower quantities in normal cells [16]. Because they are self-antigens, they are inherently less immunogenic. Candidate antigens being evaluated in ovarian cancer generally fall into this classification. A number of candidate antigens including HER2/neu, p53, CA125, MUC1, CEA, folate receptor alpha, cancer testis antigens like NY-ESO-1 and insulin growth factor binding proteins have all been proposed as potential vaccine targets in ovarian cancer due to their reported immunogenicity [17–27].

Therapeutic cancer vaccines have been evaluated using a number of platforms including peptides/protein or DNA in combination with adjuvant, anti-idiotypic vaccines, recombinant viruses or other microbes, tumor cells or tumor cell lysates, or the delivery of activated dendritic cells to patients. A number of these strategies are currently being studied for ovarian cancer and their advantages and limitations can be influenced by factors inherent to the specific platform (Table 1).

Peptide strategies are attractive because they allow the direct translation of an identified tumor associated antigen into a vaccine and precise measurement of immune responses. Peptides of a specific length and sequence can represent epitopes that may be presented on MHC molecules to effector T cells. However, peptides and proteins have limited ability to elicit balanced and durable CD4 and CD8 responses alone. Peptide and protein based vaccine platforms are usually administered with an immune modulator or adjuvant because they are only weakly immunogenic. These vaccines may only represent a portion of a tumor-associated antigen and selection of epitopes may be limited by the diversity of HLA alleles in patients that are able to recognize these epitopes. Long peptides incorporating both CD8+ and CD4+ epitopes have the potential to be more efficiently presented to T cells and have been demonstrated in vaccination targeting HPV E6 and E7 in cervical cancer [28]. This strategy has been reported in a phase 1 trial of 28 ovarian cancer patients using overlapping long peptides from a human tumor self-antigen, NY-ESO-1 with adjuvant. The vaccine was well tolerated and able to induce both cellular, CD4+ and CD8+, and antibody responses in nearly all vaccinated patients when given with a Poly-ICLC adjuvant [29].

While a peptide or protein strategy may be limited by the knowledge of and ability of a specific patient’s MHC molecules to present the selected amino acids sequences, it has the potential to target multiple antigens. Additionally, downregulation of surface MHC class I is hypothesized to be a strategy of immune evasion in a number of malignancies. A look at the feasibility of selected peptides from candidate antigens: p53, SP17, survivin, WT1, and NY-ESO-1 to be incorporated in a multiantigen vaccine was undertaken by Vermeij and colleagues. In tumor samples from 270 primary ovarian cancer patients, 93.2% overexpressed at least one of the candidate antigens. Over 70% of patients overexpressed 2 or more of the candidate antigens. The authors also found that expression of MHC class I was present in over 78% of ovarian cancers tested. This combination of findings suggests that a vaccine directing a cellular immune response against multiple target antigens may find some success in ovarian cancer [30].

<table>
<thead>
<tr>
<th>Table 1 Vaccine platforms used for ovarian cancer.</th>
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<tr>
<td><strong>Platform</strong></td>
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<tr>
<td>Peptide/protein</td>
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<tr>
<td>[19,29,68–70]</td>
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<tr>
<td>DNA</td>
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<tr>
<td>Virus/bacteria</td>
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<tr>
<td>[22,23,71]</td>
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<tr>
<td>Anti-idiotypic</td>
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<td>[34–36]</td>
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<tr>
<td>Dendritic cell</td>
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<td>[67]</td>
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<td>Whole tumor</td>
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Plasmid DNA vaccines have distinct advantages over synthetic peptides. DNA is more stable and is easy to manufacture. It can be given in a smaller volume than peptide and may be better suited to a multiantigen approach. Plasmid DNA can generate intracellular synthesis of the target antigen allowing presentation via MHC class I and has been shown to be able to stably transfect skin cells. It also is weakly immunogenic and requires the coadministration of an adjuvant, or the use of a delivery vehicle such as a gene gun or liposomes. Additionally plasmids may be modified to encode non-self antigens to enhance immunogenicity. This approach has been explored in a number of malignancies, and is currently employed in phase I clinical trial at the University of Washington as an approach to vaccinate against IGFBP-2 for the treatment of advanced or recurrent ovarian cancer in remission. Although the study is ongoing, preliminary results regarding toxicity thus far are reassuring. There have been a total of 130 adverse events in 22 patients. 95% of adverse events to date were Grades 1–2 and 5% were Grades 3–5. The one related Grade 3 event was decreased lymphocyte count, and not considered a dose limiting toxicity. In preliminary analysis for immunogenicity, 40% of patients have demonstrated new serum antibodies recognizing IGFBP-2 after completion of vaccinations (D. Cecil, personal communication).

Viral and microbial vectors have also been explored as vehicles for therapeutic cancer vaccines. Exploiting their natural immunogenicity as pathogens obviates the need for adjuvants and their genomes may be manipulated to express candidate vaccine targets. Selection of an individual vector is crucial since each possesses specific characteristics in how it is perceived by the immune system. Poxviral vectors, due to their large genome, can allow the insertion of multiple genes, up to 10 kb, which may include the target antigen or antigens and immunostimulatory factors. Poxviruses are double stranded DNA viruses that replicate in the cytoplasm of infected cells, so no viral sequences are inserted in the host genome. In a trial conducted at the National Cancer Institute, 26 patients with metastatic breast or ovarian cancer that had 3 or more prior chemotherapy regimens were vaccinated with a recombinant poxviral vaccine expressing tumor associated antigens, MUC-1 and CEA in addition to TRICOM, a set of T cell stimulatory molecules including B7.1, ICAM-1, and LFA-3. The majority of patients in this study had widely metastatic disease. Of the 14 ovarian cancer patients, the median time to progression was 2 months. While there was a degree of heterogeneity in the patients in this study, the patients who seemed to derive the most benefit from the vaccine were those that had limited tumor burden and who were not immune compromised by multiple rounds of prior chemotherapy [31].

Viral vectors have also been employed in combination to enhance immune responses through a heterologous prime boost approach. Immunization targeting NY-ESO-1 using this strategy has completed phase II trials [22]. Twenty-two ovarian cancer patients who had completed surgery and platinum based chemotherapy in complete remission were enrolled, the majority of whom were stage III or IV and optimally cytoreduced with serous histology. Patients were primed with recombinant vaccinia-NY-ESO-1 Vaccinations and subsequently boosted with recombinant fowlpox NY-ESO-1. This combination was able to increase both antibody and cellular immune recognition of NY-ESO-1. Of patients that were seronegative at baseline, 42% of patients seroconverted after vaccination. For cellular immune responses, pre-existing CD4+ and CD8+ responses were detected in 68% and 14% of patients respectively. Postvaccination, these percentages increased to 91% for CD4+ and 45% for CD8+ T cells recognizing NY-ESO-1. There were no significant toxicities greater than Grade 2. Since these patients were all without measurable disease at time of enrollment, the primary clinical endpoint was PFS, which was reported to be a median of 21 months (95% CI, 16–29 months). Overall survival was reported to be 48 months. Patients that derived the most benefit were patients who were initially seronegative and remained so, but were able to develop CD4 and/or CD8 T-cell responses, and patients were seronegative patients who seroconverted and/or developed CD4 and/or CD8 T-cell responses. There were no significant toxicities greater than Grade 2. Given that a portion of patients in this population would be expected to present with a platinum resistant recurrence within 6 months after completion of primary chemotherapy, the reported PFS is notable, in spite of the limited sample size.

Vaccination targeting non-protein antigens, such as carbohydrates, has been attempted using anti-idiotypic vaccines, which have shown to be effective in breaking immune tolerance associated with targeting tumor associated self antigens [32]. The immune system will respond to carbohydrate antigens in a T cell independent manner and antibody levels recognizing these targets have been associated with prognosis after surgery and chemotherapy in a number of malignancies [33]. In ovarian cancer, this strategy has been employed using anti-Id mAb ACA-125 or abagovomab, which mimics CA-125. A phase I/II trial with 119 patients shows improved survival (23.4 vs. 4.9 months) in patients who demonstrated antibody responses to vaccination [34]. This and subsequent reports of the safety and efficacy led to a phase III randomized trial of 888 patients with FIGO stage III or IV ovarian cancer in complete remission after primary surgery and platinum/taxane based chemotherapy in a placebo controlled multicenter study with RFS as the primary endpoint and OS and immunologic response as secondary endpoints. While measurable immune responses were reported and the monthly injections were safe, there was no benefit realized in either RFS or OS [35]. These results and those of a similar approach in another multicenter phase III trial [36] suggest that CA125 may not represent the optimal vaccine target, or that anti-idiotypic vaccination may not yield the type of immune response required, or possibly both.

Dendritic cells are antigen-presenting cells capable of initiating immune responses when they are pulsed with antigens. When in an immature state, dendritic cells are characterized by a high degree of antigen uptake. When stimulated with bacterial products, cytokines or CD40, maturation and migration to secondary lymphoid organs can occur. Here they have the ability to initiate primary immune responses in the context of MHC and costimulatory molecules. Vaccination using dendritic cells pulsed with HER-2/neu or MUC1 peptides was one of the first applications of this approach to ovarian cancer. In a phase I/II study, patients with metastatic breast and ovarian cancer expressing HLA-A2 and HER2/neu or MUC1 enrolled [37]. Dendritic cells were generated from PBMC, pulsed with peptides and injected subcutaneously on days 1, 14 and 28. Peptide specific T cell responses, evidenced by interferon gamma secretion by CD8+ lymphocytes after immunizations, were detected. Furthermore, cytotoxic assays demonstrated the ability of induced T cells to lyse HLA-A2 tumor cells expressing the target antigens. This approach has also been subsequently adapted for use by loading with tumor cell lysates, which have been shown to expand autologous tumor reactive T cell in vitro [38,39].

Use of whole tumor derivatives such as lysates to manufacture a vaccine possesses the distinct advantage of targeting both defined antigens and undefined antigens, which have the potential to expand the number of targets for an immune response [40]. This approach, however, is limited by the need to harvest a sufficient amount of tumor from a patient, which may not be feasible for specific tumors or for patients in remission, and then possibly expand them ex vivo. There may be an increased risk of autoimmunity due to the use of large numbers of self-antigens used in the vaccine. Additionally the tumor cells or cell products would need to be made immunogenic through the use of adjuvants or dendritic cells. Finally, a vaccine constructed in this fashion would have its use likely limited to a specific patient, which would require GMP facilities and be labor intensive. This approach has been reported recently in a small study in ovarian cancer patients, used in conjunction with dendritic cells and chemotherapy with bevacizumab and oral metronomic cyclophosphamide followed by lymphodepletion and adoptive cell transfer of vaccine primed T cells [41]. Vaccine induced antitumor immune responses were measured in 4 of 6 patients and there was one complete response.
The landscape of recent phase 2 and 3 trials with clinical outcomes as endpoints has shown only modest responses in the majority of trials (Table 2). The two largest phase 3 studies have been negative. A close examination of these studies reveals some important considerations that should be addressed in the next generation of vaccines. While efforts like the Cancer Genome Atlas Project will continue to uncover new potential targets for vaccines [42–44], the phenotype of immune responses elicited by vaccination will be critical. Strategies that have generated immunogenicity through measurable antibody responses to glycoproteins using vaccination have not correlated with clinical responses in phase 3 trials [35,36]. In a phase 2 trial of viral vectors targeting NY-ESO-1, which showed PFS of 21 months in stage II/IV patients with high grade serous ovarian cancer optimally debulked, the immunologic measure correlated with clinical outcome was the ability to elicit specific CD4 and/or CD8 T-cell responses [22]. Ways to modulate the immune responses generated by available platforms have the potential to both increase the efficacy of vaccines and also expand the characteristics of patients with ovarian cancer that can be treated.

What can be done to increase the efficacy of ovarian cancer vaccines?

As the field moves forward to the next generation of vaccines, combining agents that modulate the immune response with flexible platforms that can incorporate new targets as they emerge may increase effectiveness. Ovarian cancer cells have been shown to express programmed death ligand 1, a ligand for the immunosuppressive T-cell receptor PD-1, which blocks T-cell responses [5]. The expression of PD-L1, an immunoregulatory molecule, on the surface of ovarian cancer cells has been reported to be associated with poor prognosis [45]. The interaction of PD-1, expressed on adaptive immune effector cells such as CD4 and CD8 T cells, with PD-L1 on ovarian cancer associated dendritic cells has recently been reported. In a mouse model of ovarian cancer, infiltrating DCs expressed increasing levels of PD-1 and PD-L1 over time. These dual positive DCs respond poorly to signaling and are associated with the suppression of T cell activity and infiltration of tumors. Blockage of PD-1 reduced tumor burden and increased antigen specific T cell responses [46]. The blockade of the PD-1/PDL-1 pathway has emerged as a therapeutic strategy that has shown promise in a number of solid tumors including ovarian cancer [15,47], presumably by taking advantage of pre-existing anti-tumor effectors held in check by this immunoregulatory signal. These agents have completed phase 1 studies and could be applied as adjuvants to vaccination to augment induced effectors to overcome the immunosuppressive microenvironment in ovarian cancer.

Although T cells can be drawn to ovarian cancers, the functional ability of tumor infiltrating immune cells in this milieu remains an open question. The ovarian cancer tumor microenvironment has been hypothesized to be immunosuppressive. Regulatory T cells, a subset of T cells that can modulate immune responses and maintain tolerance to self-antigen, have been studied for their significance in anti-tumor immunity. Increased frequency of CD4+CD25+FoxP3+ regulatory T-cells predicts poor patient survival in ovarian cancer [6,10]. Accumulation of CXCR3+ regulatory T cells in ovarian cancers limits T cell responses capable of eliminating tumors [48]. Transient blockage of CTLA-4, a negative regulator of antitumor responses, has also been shown to augment immune-mediated tumor killing in combination with cancer vaccines [49]. Antibody blockage of CTLA-4 with ipilimumab as a single agent has already been reported to show clinical responses in advanced ovarian cancer patients previously treated with multiple chemotherapies [13]. Furthermore, blockade of both CTLA-4 and PD-1 can expand tumor infiltrating T cells and reduce the presence of regulatory T cells [50]. This has been recently shown to reverse the dysfunction of CD8 T cells in a mouse model of ovarian cancer [51]. Combining vaccines with CTLA-4 blockade, blockage of the PD-1/PD-L1 pathway, or both could provide the necessary signals to unleash vaccine-induced effector and memory cells.

In addition to these new approaches, chemotheraphy agents in current use need to be investigated in conjunction with therapeutic vaccination. Although the traditional view of chemotherapy and its impact on the immune system center on the clinical concerns of immune suppression, more and more evidence has emerged supporting immunostimulatory effects [52–55]. Chemotherapy may also recruit innate immune responses in achieving the elimination of tumor cells. Breast cancer patients with a loss of function allele in TLR4 relapse more quickly after radiation and chemotherapy than those with a wild type allele [56]. Interestingly, a number of findings address the primary agents used to treat ovarian cancer: platinum and taxanes [57]. Human cytotoxic T cells exposed to carboplatin or cisplatin in vitro at concentrations comparable to in vivo therapeutic concentrations showed no decrease in CTL mediated killing [58]. Exposure to platinum-based chemotherapy has also been shown to reduce the expression of T cell inhibitory molecule, programmed death receptor–ligand 2 (PD-L2) both on tumor cells and T cells increasing their immunostimulatory potential [59]. Paclitaxel has been reported to increase the ability of ovarian cancer cells to activate T cells via molecule complexes of polyosaccharide/ribosome-bound HER-2 polypeptides [60]. It has also been found to selectively impair regulatory T cells when used in combination with other chemotherapy agents in patients undergoing treatment for lung cancer, while augmenting the production of Th1 cytokines interferon gamma and interleukin 2 in CD4+ and CD8 T cells [61]. While the majority of clinical trials of vaccines in ovarian cancer have focused on remissions after primary treatment or in recurrent disease, these observations may open the door to the use of vaccination in conjunction with primary treatment, where up to 2 doses could conceivably be given prior surgery and the initiation of primary chemotherapy with the possibility that chemotherapy may then have an immunostimulatory benefit on elaborated antitumor effectors.

Recently, published studies and current active trials have sought to incorporate vaccines with chemotherapy in search of a synergistic effect, by specifically utilizing cytotoxic chemotherapy to modulate

Table 2
Recent phase II and III ovarian cancer therapeutic vaccine trials with clinical outcome as endpoints.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Platform</th>
<th>Trial design</th>
<th>Number of patients</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS3</td>
<td>A: peptide + adjuvant + IL-2</td>
<td>II</td>
<td>21</td>
<td>Median OS for A was 40.8 and 29.6 months for B (p = 0.26).</td>
</tr>
<tr>
<td>PS3</td>
<td>B: peptide + dendritic cells + IL-2</td>
<td>II</td>
<td>20</td>
<td>Median PFS was 4.2 for A and 8.7 months for B (p = 0.81) [19].</td>
</tr>
<tr>
<td>PS3</td>
<td>Peptide + adjuvant</td>
<td>II</td>
<td>20</td>
<td>2 out of 20 (10%) patients with PS3 specific responses induced by vaccination achieved stable disease [68].</td>
</tr>
<tr>
<td>PS3</td>
<td>Peptide + adjuvant + cyclophosphamide</td>
<td>II</td>
<td>10</td>
<td>2 out of 10 patients (20%) achieved stable disease [66].</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>Viral vector</td>
<td>II</td>
<td>22</td>
<td>Mean PFS was 21 months (95% CI, 16–25)</td>
</tr>
<tr>
<td>CA125</td>
<td>Anti-idiotypye</td>
<td>III</td>
<td>373</td>
<td>Mean OS was 48 months [22].</td>
</tr>
<tr>
<td>CA125</td>
<td>Anti-idiotypye</td>
<td>III</td>
<td>888</td>
<td>Mean time to relapse was 10.3 months compared to 12.9 months for placebo (p = 0.29, log-rank test) [36]. Hazard ratio of PFS 1.099 (95% CI, 0.919–1.315), p = 0.301.</td>
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<td></td>
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<td>Hazard ratio of OS 1.150 (95% CI, 0.872 to 1.518), p = 0.322 [35].</td>
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</table>
the effects of regulatory T cells. Metronomic cyclophosphamide has also been found to deplete regulatory T cells, induce type I interferon, and synergize with vaccination [62–65]. Peptide vaccination targeting p53 in combination with IV cyclophosphamide was studied in a single arm phase II trial. Vaccine induced T cells secreting interferon gamma in response to p53 were found in 9 of 10 patients after 2 vaccinations, all of which were preceded with cyclophosphamide infusion. Although this study did not show a quantitative decrease in regulatory T cells as a result of cyclophosphamide, the induction of activated specific T cell was significantly higher than prior groups treated in the same fashion without cyclophosphamide. Stable disease was achieved in 2 out of 10 patients [66]. Dendritic cell vaccination with and without cyclophosphamide was also reported in a phase I/II trial of advanced ovarian cancer patients in remission. 14 total patients were enrolled in this trial. Patients were randomized to groups with and without cyclophosphamide prior to vaccination with peptide loaded dendritic cells. Peptides represented Her2/neu, hTERT and PADRE. There was no reduction in regulatory T cells with cyclophosphamide and no change in total lymphocytes. But patients show significant immunosuppression with below normal response to components of the pneumococcal vaccine. Three year overall survival was 90% and T cell responses were measured to HER2/neu and hTERT peptides [67]. While these initial efforts to incorporate cyclophosphamide with vaccines have not shown significant effects on regulatory T cells and immune responses, it is important to note that both trials used cyclophosphamide as an intravenous infusion of 300–500 mg/m2. Most studies show that regulatory T cell levels can recover 1–2 weeks after IV infusion [65]. Oral metronomic cyclophosphamide that has been shown to decrease regulatory T cells is given at much lower doses, 50 mg twice a day, with one week on and one week off for a month or more [62].

The efficacy of a therapeutic ovarian cancer vaccine will likely rest with factors that govern the elicited antitumor immune response: the quality of the chosen target antigen or antigens, the vaccine platform or vector, and the selection of patient population either by clinical factors or tumor expression profiling. While some of these factors are restricted by inherent limitations, immunomodulation of vaccines using adjuvants presents the ability to modify vaccines to direct the resulting phenotype of the immune response toward the ones favoring the elimination of tumor. By advancing research in the use of agents that can modulate the tumor microenvironment, vaccines may be able to overcome the roadblocks set up by ovarian cancers to derail the propagation of an effective anti-tumor immune response.

Conflict of interest statement
Dr. Liao has no conflicts of interest to declare. Dr. Disis is an inventor on patents held by the University of Washington that pertain to data presented in the review.

Acknowledgements
Dr. Liao is a scholar supported by the National Institutes of Health’s Women’s Reproductive Health Research Program at the University of Washington (5K12HD001264). Dr. Liao is also supported by the Marsha Rivkin Center for Ovarian Cancer Research. Dr. Disis is the Athena Distincti- fied Professor of Breast Cancer Research and supported by P50CA083636 for this work. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References
can be found on the next page.
advanced stage ovarian cancer. J Immunother May 2008;31(4):420–30 [Clinical Trial, Phase I Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov’t].
